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Venous Thromboembolism Prophylaxis in Orthopedic Surgery



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Venous Thromboembolism Prophylaxis in Orthopedic Surgery

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Prepared by:

University of Connecticut/Hartford Hospital Evidence-based Practice Center
Hartford, CT

Principal Investigators:

Diana M. Sobieraj, Pharm.D.
Craig I. Coleman, Pharm.D.
Vanita Tongbram, M.B.B.S., M.P.H.
Soyon Lee, Pharm.D.
Jennifer Colby, Pharm.D.
Wendy T. Chen, Pharm.D.
Sagar S. Mekanji, Pharm.D.
Ajibade Ashaye, M.D., M.P.H.
Jeffrey Kluger, M.D., F.A.C.C.
C. Michael White, Pharm.D., FCP, FCCP

Evidence-based Practice Center Directors:

C. Michael White, Pharm.D., FCP, FCCP
Craig I. Coleman, Pharm.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Mary P. Nix, M.S, M.T. (ASCP) SBB, PMP
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Key Informants and Technical Expert Panel

Craig Della Valle, M.D.
Associate Professor of Orthopaedic Surgery
Rush University Medical Center
Chicago, IL

Charles W. Francis, M.D.
Director, Hemostasis and Thrombosis
Program
University of Rochester School of Medicine
& Dentistry
Rochester, NY

Jay Lieberman, M.D.
Director of the New England
Musculoskeletal Institute
Chairman of the Department of Orthopaedic
Surgery
University of Connecticut Health Center
Farmington, CT

Charles M. Turkelson, M.D.
Director, Department of Research and
Scientific Affairs
American Academy of Orthopaedic Surgery
Rosemont, IL

Yngve Falck-Ytter, M.D.
Assistant Professor of Medicine
Case Western Reserve University
School of Medicine
Director of Hepatology, Gastroenterology
Section, Department of Medicine
Louis Stokes VA Medical Center
Cleveland, OH

Joshua J. Jacobs, M.D.
The William A. Hark, M.D. - Susanne G.
Swift Professor and Chairman
Department of Orthopaedic Surgery
Rush Medical College
Chicago, IL

J. Samuel Pope, M.D.
Department of Pulmonary Medicine
Hartford Hospital
Hartford, CT

Sandra Zelman Lewis, Ph.D.
Assistant Vice President, Health & Science
Policy
American College of Chest Physicians
Northbrook, IL

Peer Reviewers

Olivia J. Phung, Pharm.D.
Western University of Health Sciences
Pomona, CA

Sarah Spinler, Pharm.D., F.C.C.P.,
F.A.H.A., B.C.P.S. (AQ Cardiology)
University of the Sciences in Philadelphia
Philadelphia, PA

Paul Lotke, M.D.
Hospital of the University of Pennsylvania
Philadelphia, PA

Venous Thromboembolism Prophylaxis in Orthopedic Surgery

Structured Abstract

Objectives. This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) examining the comparative efficacy and safety of prophylaxis for venous thromboembolism in major orthopedic surgery (total hip replacement [THR], total knee replacement [TKR], and hip fracture surgery [HFS]) and other nonmajor orthopedic surgeries (knee arthroscopy, injuries distal to the hip requiring surgery, and elective spine surgery).

Data Sources. Medline, the Cochrane Central Register of Controlled Trials, and Scopus from 1980 to May 2011 with no language restrictions.

Review Methods. Controlled trials of any size and controlled observational studies with ≥ 750 subjects were included in our comparative effectiveness review if they were in patients undergoing one of six a priori defined orthopedic surgeries; provided data on prespecified intermediate, final health, or harms outcomes; defined deep vein thrombosis (DVT) and pulmonary embolism (PE) according to rigorous criteria (where applicable), and included prophylactic products (pharmacologic or mechanical) available in the United States. Using predefined criteria, data on study design, interventions, quality criteria, study population, baseline characteristics, and outcomes were extracted. All of the available data were qualitatively evaluated and where possible, statistically pooled. We used random effects derived relative risks (RR) for most analyses and Peto's Odds Ratios (OR) in comparisons of rare events both with 95 percent confidence intervals (CIs). I^2 was used to detect statistical heterogeneity and Egger's weighted regression statistics were used to assess for publication bias. The strength of evidence (SOE) and applicability of evidence (AOE) for each outcome was rated as insufficient (I), low (L), moderate (M), or high (H).

Results. In major orthopedic surgery (THR, TKR, and HFS, respectively), the incidence of DVT (39 percent, 53 percent, 47 percent), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), and minor bleeding (5 percent, 5 percent, not reported) were reported in the placebo/control groups of clinical trials. The SOE and AOE were predominantly low for THR and TKR and was insufficient HFS. In major orthopedic surgery, pharmacologic prophylaxis reduced major venous thromboembolism (VTE) (OR 0.21 [0.05 to 0.95], SOE: L, AOE: L), DVT (RR 0.56 [0.47 to 0.68], SOE: M, AOE: L), and proximal DVT (pDVT) (RR 0.53 [0.39 to 0.74], SOE: H, AOE: L), but increased minor bleeding (RR 1.67 [1.18 to 2.38], SOE: H, AOE: M). Prolonged prophylaxis for ≥ 28 days was superior to prophylaxis for 7 to 10 at reducing symptomatic objectively confirmed VTE (RR 0.38 [0.19 to 0.77], SOE: M, AOE: L), PE (OR 0.13 [0.04 to 0.47], SOE: H, AOE: L), DVT (RR 0.37 [0.21 to 0.64], SOE: M, AOE: M), and pDVT (RR 0.29 [0.16 to 0.52], SOE: H, AOE: M) but increased minor bleeding (OR 2.44 [1.41 to 4.20], SOE: H, AOE: M). Using both pharmacologic and mechanical prophylaxis reduced DVT (RR 0.48 [0.32 to 0.72] SOE: M, AOE: M) versus pharmacologic prophylaxis alone.

Low molecular weight heparins (LMWHs) reduced PE (OR 0.48 [0.24 to 0.95], SOE: M, AOE: L), DVT (RR 0.80 [0.65 to 0.99], SOE: M, AOE: L), pDVT (RR 0.60 [0.38 to 0.93], SOE: H, AOE: L), major bleeding (OR 0.57 [0.37 to 0.88], SOE: H, AOE: L), and heparin induced thrombocytopenia (OR 0.12 [0.03 to 0.43], SOE: M, AOE: L) versus unfractionated heparin. LMWHs reduced DVT (RR 0.66 [0.55 to 0.79], SOE: L, AOE: M) but increased major bleeding (RR 1.92 [1.27 to 2.91], SOE: H, AOE: M), minor bleeding (RR 1.23 [1.06 to 1.43], SOE: M, AOE: M), and surgical site bleeding (OR 2.63 [1.31 to 5.28], SOE: L, AOE: L) versus vitamin K antagonists. LMWHs increased DVT (RR 1.99 [1.57 to 2.51], SOE: M, AOE: L) and pDVT (OR 2.19 [1.52 to 3.16], SOE: L, AOE: L) but reduced major bleeding (OR 0.65 [0.48 to 0.89], SOE: M, AOE: L) versus factor Xa inhibitors. Antiplatelets increased DVT (1.63 [1.11 to 2.39], SOE: M, AOE: L) versus mechanical prophylaxis. Unfractionated heparin increased DVT (RR 2.31 [1.34 to 4.00], SOE: M, AOE: L) and pDVT (OR 4.74 [2.99 to 7.49], SOE: M, AOE: L) versus direct thrombin inhibitors. Intermittent compression stocking decreased DVT (RR 0.06 [0.01 to 0.41], SOE: L, AOE: L) versus graduated compression stockings. We did not have adequate information to evaluate the role of inferior vena cava filter (IVC) filters or to evaluate the impact of prophylaxis on nonmajor orthopedic surgeries.

Conclusions. In major orthopedic surgery, while the risk of developing deep vein thrombosis is highest followed by pulmonary embolism and major bleeding, there are inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism or is an independent predictor of pulmonary embolism. The balance of benefits to harms is favorable for providing prophylaxis to these patients and to extend the period of prophylaxis beyond the standard 7–10 days. The comparative balance of benefits to harms for LMWHs are superior to unfractionated heparin. Other interclass comparisons either could not be made due to lack of data, showed similarities between classes on outcomes, or had offsetting effects where benefits of one class on efficacy was tempered by an increased risk of bleeding. The balance of benefits to harms for combined pharmacologic plus mechanical prophylaxis versus either strategy alone could not be determined. We could not determine the impact of IVC filters on outcomes or the impact of prophylaxis on the nonmajor orthopedic surgeries evaluated.

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Executive Summary

Background

Major orthopedic surgery describes three surgical procedures including total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery (HFS). As a whole, major orthopedic surgery carries a risk for venous thromboembolism (VTE), and therefore, a variety of strategies to prevent VTE are available. Such strategies include pharmacological (antiplatelet, anticoagulant) and mechanical modalities that can be used alone or in combination.¹ However, prophylaxis with pharmacologic strategies also has limitations, including the risks of bleeding and prosthetic joint infections and the potential need for reoperation.

While prophylactic strategies may decrease the risk of VTE, deep vein thrombosis (DVT), and pulmonary embolism (PE) in major orthopedic surgery, the impact of VTE prophylaxis on orthopedic surgeries including knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery has not been sufficiently evaluated. The magnitude of benefit and harms in contemporary practice with the use of rigorous endpoint definitions and evaluation of pharmacologic agents or devices available within the United States amongst the orthopedic surgery population is not well known. Additionally, the impact of duration of prophylaxis on outcomes, whether dual prophylactic therapy is superior to single modality therapy, and the comparative effectiveness of different pharmacologic or mechanical modalities have not been adequately systematically reviewed. Lastly, in contemporary practice, the risks of VTE, PE, and DVT and the causal link between DVT and PE have not been well established.²

Objectives

To perform a comparative effectiveness review examining the benefits and harms associated with VTE prophylaxis in patients undergoing major orthopedic surgery and other orthopedic surgeries including knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery, we sought to answer the following 11 Key Questions (KQs):

KQ 1: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of VTE and bleeding outcomes in contemporary practice?

KQ 2: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what patient, surgical, or postsurgical characteristics predict or differentiate patient risk of VTE and bleeding outcomes in contemporary practice?

KQ 3: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring intermediate outcomes, such as DVT (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?

KQ 4: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, post thrombotic syndrome (PTS), mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion,

heparin-induced thrombocytopenia (HIT), discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins [LMWHs], injectable unfractionated heparin [UFH], injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors [DTIs], oral vitamin K antagonists [VKAs]) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump).

KQ 5: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable LMWHs, injectable UFH, injectable or oral factor Xa inhibitors, injectable or oral DTIs, oral VKAs, and mechanical interventions.

KQ 6: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), what is the comparative efficacy of individual agents within classes (LMWH and mechanical devices) on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

KQ 7: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

KQ 8: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

KQ 9: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava (IVC) filter placement compared with any external mechanical intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT,

major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, reoperation, and IVC filter placement associated insertion site thrombosis?

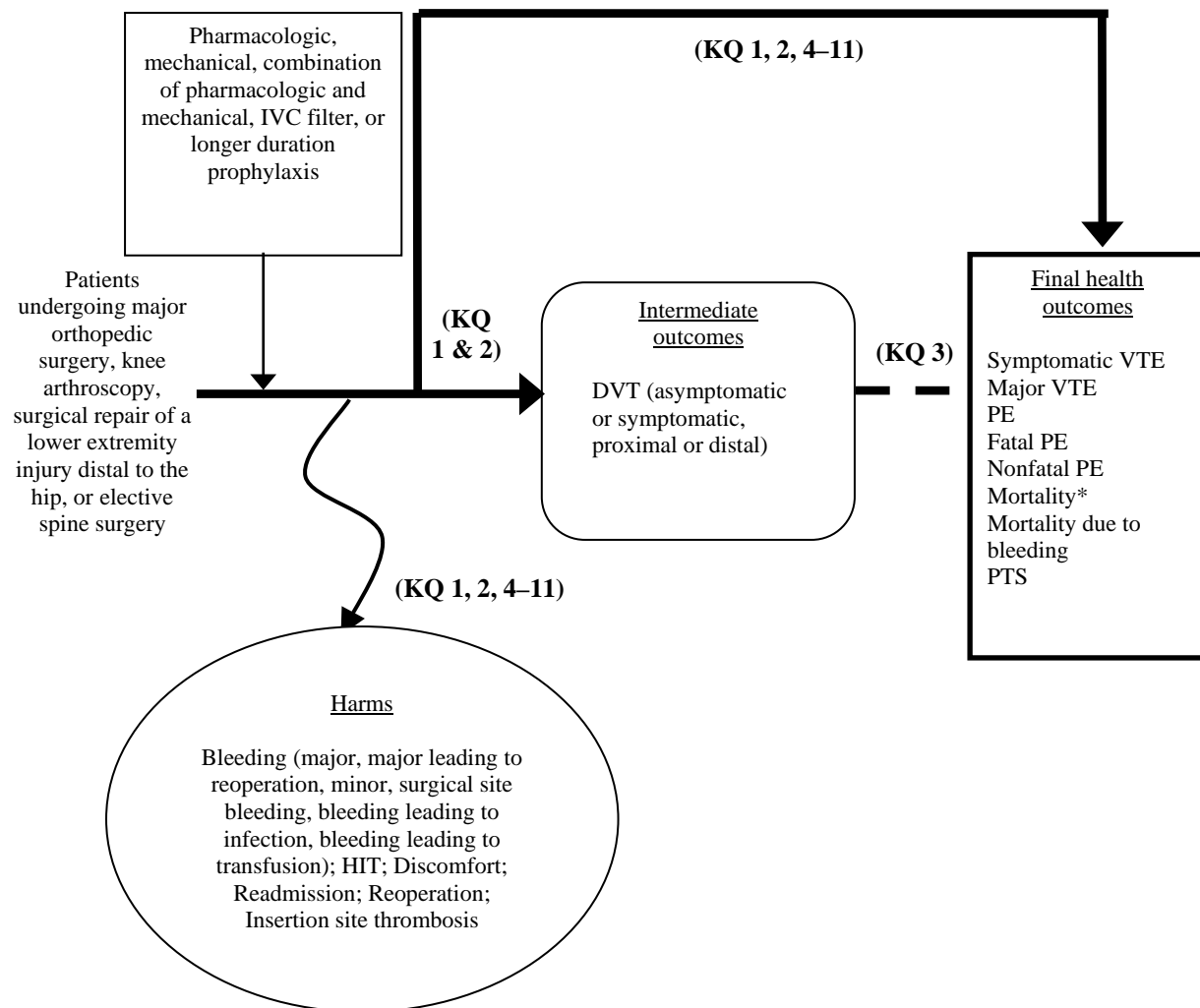
KQ 10: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

KQ 11: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of injectable antithrombotic agents (LMWH vs. UFH vs. factor Xa inhibitors vs. DTIs) compared with mechanical interventions on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

The analytic framework for this report is presented in Figure A.

Analytic Framework

Figure A. Analytic framework for the comparative effectiveness of venous thromboembolism prophylaxis in orthopedic surgery



*Mortality is all-cause mortality

DVT = deep vein thrombosis; HIT = heparin-induced thrombocytopenia; IVC = inferior vena cava; PE = pulmonary embolism; PTS = post thrombotic syndrome; VTE = venous thromboembolism

Methods

Input From Stakeholders

The Evidence-based Practice Center drafted a topic refinement document with proposed KQs after consulting with Key Informants. Our Key Informants included eight physicians: three provided the orthopedic surgeon's perspective, one of which was a local expert; one provided a local pulmonologist's perspective; two provided expertise in methodology/guideline development; one provided a hematologist's perspective; and one provided expertise in health policy. There was equal representation from both the American College of Chest Physicians and

the American Academy of Orthopedic Surgeons (three members each). Our Key Informants did not have financial or other declared conflicts. The public was invited to comment on the topic refinement document and KQs. After the public commentary, responses to public commentary, and proposed revisions to the KQs were reviewed, a preliminary protocol was generated and reviewed with the Technical Expert Panel. The aforementioned Key Informants constituted the Technical Expert Panel and provided feedback on the feasibility and importance of our approach and provided their unique insight. Again, no conflict of interest was identified. The draft comparative effectiveness review report underwent peer review and public commentary, and revisions were made before being finalized.

Data Sources and Selection

A systematic literature search of Medline, the Cochrane Central Register of Controlled Trials, and Scopus from 1980 to September 2010 was conducted with no language restrictions. The year 1980 was used as a restriction to reflect contemporary practice. Two separate literature searches were conducted. The first search was used to identify studies that evaluated pharmacologic, mechanical, or inferior vena cava filter methods of thromboprophylaxis in patients undergoing major orthopedic surgery, describe the association between patient, surgical, or postsurgical characteristics and VTE or bleeding, or describe the association between intermediate and final health outcomes to answer KQs 1 through 9. The second search was used to identify studies which evaluate pharmacologic or mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery to answer KQs 10 and 11. Backward citation tracking was also conducted. A grey literature search of regulatory documents, abstracts, and ongoing clinical trials was conducted by the Scientific Resource Center and reviewed by two independent investigators for inclusion into our literature base by applying the same a priori defined inclusion criteria defined below. The literature searches were updated in May 2011.

Two independent investigators assessed studies for inclusion in a parallel manner based on a priori defined criteria. In evaluating all KQs, randomized controlled trials (RCTs) of any size or controlled observational studies (case controlled or cohort studies) enrolling at least 750 patients were included if they explicitly reported the use of imaging studies to confirm VTE events (Doppler ultrasound or venography for DVT and spiral computed tomography [CT] angiography or ventilation/perfusion [V/Q] scan with either Prospective Investigation of Pulmonary Embolism Diagnosis [PIOPED] criteria or high clinical suspicion based on symptoms for PE). Observational studies that enrolled fewer than 750 subjects were excluded because numerous RCTs in this literature base enroll over 500 participants, with the most contemporary trials enrolling over 1,000 participants. Therefore observational studies would need to be of larger size to provide additional valuable information on outcomes of interest and applicability. Additional inclusion criteria were used specific to each KQ and are stated below.

For KQ 1 and KQ 2, only RCTs and observational studies of patients undergoing major orthopedic surgery (TKR, THR, HFS) that included an outcome of interest were included. For efficacy outcomes in KQ 1, only placebo or control arms of RCTs and observational studies were eligible, while for bleeding these arms or mechanical prophylaxis arms were eligible; so that the natural incidence of outcomes could be reported. For KQ 2, RCTs and observational studies needed to describe the association of patient, surgical or postsurgical characteristics with an outcome and made adjustments for confounding (randomization, multivariable logistic regression, or propensity score matching/adjustment). For KQ 3, only RCTs or observational

studies of patients undergoing major orthopedic surgery (TKR, THR, HFS) were included if they evaluated pharmacologic VTE prophylactic methods or reported the predictors of PE and reported data on both PE (asymptomatic or symptomatic) and DVT (asymptomatic or symptomatic).

For KQs 4 through 9, RCTs and observational studies had to compare pharmacologic or mechanical methods of thromboprophylaxis versus control or with each other, compare combination pharmacologic and mechanical methods of thromboprophylaxis with one or the other strategy, or compare use of an inferior vena cava filter with mechanical methods of thromboprophylaxis; and report data on at least one prespecified outcome. Studies had to evaluate only major orthopedic surgery or report results of major orthopedic surgery separately from other surgeries. RCTs and observational studies included in KQ 10 and KQ 11 needed to report on a prespecified outcome and compare pharmacologic or mechanical methods of thromboprophylaxis. Studies had to evaluate only patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion with or without decompression, laminectomy, or discectomy all of the lumbar region) or report the results of these nonmajor orthopedic surgeries separately.

Data Extraction and Quality Assessment

Two reviewers used a standardized data extraction tool to independently extract study data with disagreements resolved through discussion. The following data were collected: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, patient baseline, surgical and postsurgical characteristics, thromboprophylaxis regimen, mobilization status of the patients, use of concurrent standard medical therapies, and data needed to assess intermediate and final health outcomes and adverse events.

Validity assessment was performed using the recommendations in the Evidence-based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews.³ Each study was assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of outcome assessors, intent to treat analysis, description of participant withdrawals (percent followup), and potential conflict of interest. Additionally, RCTs were assessed for randomization technique and allocation concealment. Observational studies were assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were given an overall score of good, fair, or poor.

For applicability assessment, effectiveness studies met five of the following seven criteria: orthopedic surgery population, less stringent eligibility criteria, assessed final health outcomes, adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention to treat analysis. Studies meeting less than five criteria would be classified as efficacy trials and deemed to have less applicability. Specific patient, intervention, comparator, outcome, and setting factors that limit applicability were also evaluated and extracted to derive a determination of individual study applicability.

Data Synthesis and Analysis

We conducted meta-analyses when two or more RCTs adequate for pooling were available for any outcome. Data from observational studies were not pooled. For dichotomous outcomes, weighted averages were reported as proportions (KQ 1 only), Peto's odds ratios (OR) or relative risks with associated 95 percent confidence intervals. Peto's OR was chosen over relative risk when the control event rate was exceptionally low (less than 5 percent) and the number of subjects randomized in each group of a trial was similar in the majority of trials within the given analysis.⁴ As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model was used (except for Peto's OR). Statistical heterogeneity was addressed using the I^2 statistic. Egger's weighted regression statistics was used to assess for publication bias. Statistics were performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England).

We used EPC GRADE (Grading of Recommendations Assessment, Development) to assess the strength of evidence.⁵ This system uses four required domains (risk of bias, consistency, directness, and precision) and classifies into four broad categories: high, moderate, low, or insufficient grade. Additional optional domains were not determined to be necessary and were not utilized. The applicability of evidence was rated into the same categories qualitatively based on the conglomeration of the individual studies applicability.

Results

Results of searches one and two are given in Figures B and C. Of the 177 articles included in search one, 120 articles represented 97 unique randomized controlled trials (N=44,214)⁶ and 14 articles represented 13 unique controlled observational studies (N=480,241).⁶ Thirty-nine citations represented 39 systematic reviews/meta-analyses.⁶ Systematic reviews and meta-analyses were used to manually search for additional references as well as to compare results of our meta-analyses with previously published similar analyses.

The second literature search yielded two unique randomized controlled trials (N=235)⁶ and four articles representing three unique meta-analyses.⁶

A summary of results with ratings of the strength and applicability of evidence for KQs 1 through 8 can be found in Table A. Only evaluations rated with a strength of evidence of low, moderate, or high are included in the table. Evaluations for KQs 9 through 11 had insufficient strength of evidence.

KQ 1: Data were limited to placebo or control arms of trials for PE and DVT outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native postoperative incidence of DVT events was highest followed by PE and bleeding events. Followup periods were defined in most trials as the postoperative period and may imply a more immediate rather than longer term followup. The strength of evidence is predominately low for outcomes evaluated in hip and knee replacement surgery while all outcomes in hip fracture surgery were rated with insufficient evidence. Not all three surgeries had incidence data reported in clinical trials; therefore, the symbol "--" is used when no data were reported for the given surgery and outcome. In THR, TKR, and HFS, respectively, the incidences were: DVT (39 percent, 46 percent, 47 percent), proximal DVT (32 percent, 17 percent, --), distal DVT (30 percent, 22 percent, --), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (5 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0

percent, 0 percent, --). Statistically significant levels of publication bias were detected for major bleeding and minor bleeding in THR, suggesting an underestimation of the incidence, which directionality of publication bias for proximal DVT in THR was unclear. Although RCTs and studies that used objective diagnostic means to confirm efficacy outcomes were included as opposed to less rigorous criteria, a high degree of heterogeneity was present for most outcomes. This may be due to additional factors, such as different definitions of events, different ethnicities and countries in which trials were conducted, and undefined periods of postoperative followup and variation in duration of followup, potentially leading to insufficient length of followup for the outcomes being assessed. Our results are similar to that of previous pooled analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001, in which 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding.

KQ 2: Several RCTs identified through our literature search evaluated different surgical characteristics on outcomes of interest, including anesthetic regimen, cemented arthroplasty, tourniquet use, limb positioning, and fibrin adhesive use. However, few trials evaluated each characteristic and subsequently did not address all major orthopedic procedures. Additionally, most trials evaluated intermediate health outcomes and did not address final health outcomes, and only one trial evaluated bleeding outcomes. As such, pooling was not possible. The surgical comparison with the most identified data was general anesthesia versus regional anesthesia. The impact of general versus regional anesthesia on several measures of DVT (overall, asymptomatic, proximal) was favorable to neutral for regional anesthesia while distal and symptomatic DVT, PE, and major bleeding were neutral. In a previous meta-analysis of 21 studies, regional anesthesia was associated with nonsignificantly reduced odds of pulmonary embolism and significantly reduced odds of deep vein thrombosis with no real impact on mortality versus general anesthesia. Although one trial compared spinal versus epidural anesthesia on the risk of deep vein thrombosis, no events occurred in the groups compared. The other characteristics were too limited to make any determinations.

Patient characteristics were primarily evaluated in multivariate regression analyses of observational studies. Few characteristics were evaluated in multiple studies, and oftentimes when a significant finding was observed, the magnitude or direction of the effect was not reported. Patient characteristics found to significantly increase the odds of symptomatic objectively confirmed VTE in all available studies included congestive heart failure (two studies), inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric fracture (one study), subtrochanteric fracture (one study), increased hemoglobin (one study), personal or familial history of VTE, (one study), and varicose veins (one study). Patient characteristics found to increase the odds of PE (evaluated in one study each) included age and genitourinary infection while cardiovascular disease was found to decrease the odds of PE. The following characteristics showed a mixed effect on DVT: age (two studies showed a significant increase while one study showed no effect), obesity (one study showed a significant increase while one study showed no effect), and gender (one study showed a significant increase in females while one study showed gender had no effect). Metabolic syndrome increased the odds of symptomatic DVT while congestive heart failure increased the odds of proximal DVT in the single study that evaluated each covariate. The one study that evaluated harms (major bleeding) suggested that age, gender, risk of bleeding, specific surgical procedure (total hip, knee replacement or hip fracture surgery), and prophylaxis administered in

the hospital significantly impacted the risk of major bleeding. However, the magnitude and direction of the effect was not specified.

KQ 3: Pulmonary embolism was the only final health outcome with data depicting the relationship to the intermediate outcome DVT. In one observational study in TKR surgery, the overall occurrence of PE and the subset with symptomatic PE occurred more frequently in those with DVT. However, the data were not adjusted for confounders, and we cannot discern whether these variables are correlated or colinear. No trials or studies were available assessing whether DVT was correlated with or a multivariate predictor of PE. This data may be limited because the routine use of prophylaxis may have reduced the occurrence of DVT and the scheduled anticoagulant treatment for DVT, once it was detected, may have diminished the percentage that developed into PE.

KQ 4: Providing pharmacologic prophylaxis versus no prophylaxis has a better comparative balance of benefits and harms. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreased risk of proximal and distal DVT (relative risk reduction [RRR] 47 percent and 41 percent, respectively), with moderate evidence for the decrease in DVT overall and asymptomatic DVT (RRR 44 percent and 48 percent, respectively) in patients undergoing major orthopedic surgery. Higher levels of statistically heterogeneity were detected for the evaluation of DVT ($I^2=52.8$ percent). Statistically significant publication bias was detected in the evaluation of proximal DVT, suggesting an underestimation of benefit. There is low evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major VTE in patients undergoing major orthopedic surgery (RRR 79 percent). Pharmacologic prophylaxis did not significantly impact PE versus no prophylaxis, although it was trending in that direction, and significantly reduced the risk of PE when the analysis was limited to the most stringent trials in which background prophylaxis (such as compression stockings) was not allowed in the experimental groups. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding (relative risk increase 67 percent), and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis did not significantly impact nonfatal PE, mortality, symptomatic DVT, or major bleeding in patients undergoing major orthopedic surgery. Our results are in general agreement with the six previous meta-analyses of trials comparing pharmacologic prophylaxis versus placebo/control in patients with major orthopedic surgery. We could not determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group.

Providing mechanical prophylaxis versus no prophylaxis may have a better comparative balance of benefits and harms, but more data are needed to support this assumption. One RCT found that mechanical prophylaxis versus no prophylaxis significantly decreased the occurrence of DVT in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal DVT in patients undergoing major orthopedic surgery, the power to detect these differences was low. In the only previous meta-analysis comparing mechanical prophylaxis (intermittent pneumatic compression and venous foot pump) versus control, the risks of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduced. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use, so benefits would likely overwhelm the risk of harms.

KQ 5: While we sought to determine the impact of therapy on numerous outcomes, we were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, either there was a lack of evaluable data or no significant differences were found. Variable levels of statistical heterogeneity were detected in the base case analyses, and in a few cases, heterogeneity improved when each surgery was evaluated separately in subgroup analysis while other times the heterogeneity increased. However, in the majority of cases, the number of trials in a subgroup analysis was too low to evaluate statistical heterogeneity. We could not determine if this means that there is a lack of effect versus a lack of power to show that it is significant. The results of previous meta-analyses are in general agreement with the findings of our comparative effectiveness review.

When compared directly with UFH, LMWH agents, as a class, have a better comparative balance of benefits and harms with significantly fewer PEs, DVTs, proximal DVTs, major bleeding, and HIT events. A higher level of statistical heterogeneity was detected in the evaluation of PE. The comparative balance of benefits and harms for LMWHs with other classes could not be readily determined. LMWH agents were also superior to VKAs at reducing measures of DVT (any, asymptomatic, proximal, and distal) but increased major, minor, and surgical site bleeding. A higher level of statistical heterogeneity was detected in the evaluation of DVT as was the presence of publication bias, which suggested an underestimation of the benefit of LMWH. Since no significant differences were found in important final health outcomes, the relevance of these reductions in DVT needs to be considered. LMWHs may be inferior to factor Xa inhibitors in terms of any, proximal, and distal DVTs but have a lower risk of major and minor bleeding. A higher level of statistical heterogeneity was detected in the evaluation of proximal DVT and major bleeding. Observational data suggested LMWH agents had decreased mortality, although this was not supported by data pooled from RCTs, which showed no significant difference. Comparing LMWH agents with DTIs is difficult because the occurrence of DVT was greater, but the occurrence of distal DVT was less with LMWHs, and while surgical site bleeding is higher LMWH therapy, the overall risk of serious bleeding was not significantly altered. Finally, when LMWH agents were compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving LMWHs.

It is difficult to discern the comparative balance of benefits and harms for oral antiplatelet therapy versus mechanical prophylaxis or VKAs. Oral antiplatelet therapy had significantly greater occurrence of any and distal DVT versus mechanical prophylaxis. In a controlled observational study, oral VKAs had significantly fewer fatal PE events versus oral antiplatelet agents. In the only available RCT comparing VKAs to oral antiplatelet agents, the same direction of effect was found, suggesting VKA superiority, but this was not significant. Mortality was higher in patients receiving aspirin versus warfarin in one observational study and was nonsignificantly trending in that direction in another observational study, but showed no difference in a clinical trial.

UFH, which was found to be inferior to LMWH agents in the balance of benefits and harms, had a greater occurrence of death and major bleeding versus factor Xa inhibitors in an observational study (with no clinical trial data to support or refute the findings), had a greater occurrence of any and proximal DVT versus DTIs, and had a greater occurrence of DVT versus mechanical prophylaxis. As such, it is likely inferior to factor Xa inhibitors in the balance of benefits and harms as well.

Patients receiving VKAs had less occurrence of proximal DVT versus mechanical prophylaxis, but with no other differences in other health outcomes or bleeding, it is hard to discern a difference in the balance of efficacy to harms between them.

KQ 6: For both LMWHs and mechanical devices, there were no significant differences in PE (any, fatal, and nonfatal), mortality, and mortality due to bleeding between modalities within a class, but these evaluations were based on one or two trials with either no events or a very low number of events.

The balance of benefits and harms from using enoxaparin versus another low molecular weight heparin within the class (dalteparin or tinzaparin) is similar. No difference in the occurrence of DVT or proximal DVT occurred between LMWHs (enoxaparin versus either tinzaparin or dalteparin). No significant difference was seen in asymptomatic DVT between enoxaparin and dalteparin, symptomatic DVT between enoxaparin and tinzaparin, or distal DVT between enoxaparin and tinzaparin. For major bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. For surgical site bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For HIT, one trial found no significant difference between enoxaparin and tinzaparin for this outcome.

The balance of benefits and harms for different mechanical modalities within a class could not be determined with the current literature base. The Venaflow pneumatic compression device significantly reduced the occurrence of DVT or distal DVT versus the Kendall pneumatic compression device in the only trial but did not significantly reduce proximal DVT.

Intermittent compression stockings significantly reduced the occurrence of DVT or distal DVT versus graduated compression stockings but did not significantly reduce proximal DVT.

In the only observational study, two intermittent compression devices were compared (ActiveCare system vs. Flowtron excel pump) and found to have a similar occurrence of DVT. Harms were not assessed in these trials or observational studies.

KQ 7: The balance of benefits and harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic surgery could not be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis did not significantly impact nonfatal PE, mortality, or DVT subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There was moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of DVT versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes could not be determined.

KQ 8: Prolonged prophylaxis had a better comparative balance of benefits and harms versus short-term prophylaxis in patients undergoing major orthopedic surgery. The impact of prolonging prophylaxis for 28 days or longer on events was compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. Prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed VTE, PE (overall and nonfatal), and DVT (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. Statistically significant publication bias was detected in the evaluation of distal DVT and nonfatal PE although the directionality was unclear. While higher heterogeneity was found for symptomatic VTE and DVT, the direction of effect was consistent among all of the trials. In base

case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis. Four previous meta-analyses compared the impact of longer versus shorter duration pharmacologic prophylaxis and are in general agreement with our present comparative effectiveness review.

KQ 9: There were no trials or studies that met our inclusion criteria.

KQ 10: One trial was available for Achilles tendon rupture and for knee arthroscopy, but no literature met inclusion criteria for elective spine surgery. Both of the available trials were small in size leading to limited power to detect differences between the groups compared. The comparative balance of benefits and harms for dalteparin therapy versus placebo or control was difficult to discern based on the scant data. In patients who had surgical repair of Achilles tendon rupture, the use of dalteparin versus placebo for 6 weeks did not significantly impact the incidence of total or proximal DVT. No patients developed a PE or major bleeding. In patients who had arthroscopic knee surgery, the use of dalteparin versus control led to significantly fewer patients with total or distal DVT. One patient in the dalteparin group developed a PE and also had a DVT. No patients had major bleeding, and the occurrence of minor bleeding was not significantly different between the two groups.

KQ 11: There were no trials or studies that met our inclusion criteria.

Figure B. PRISMA flow diagram for search one

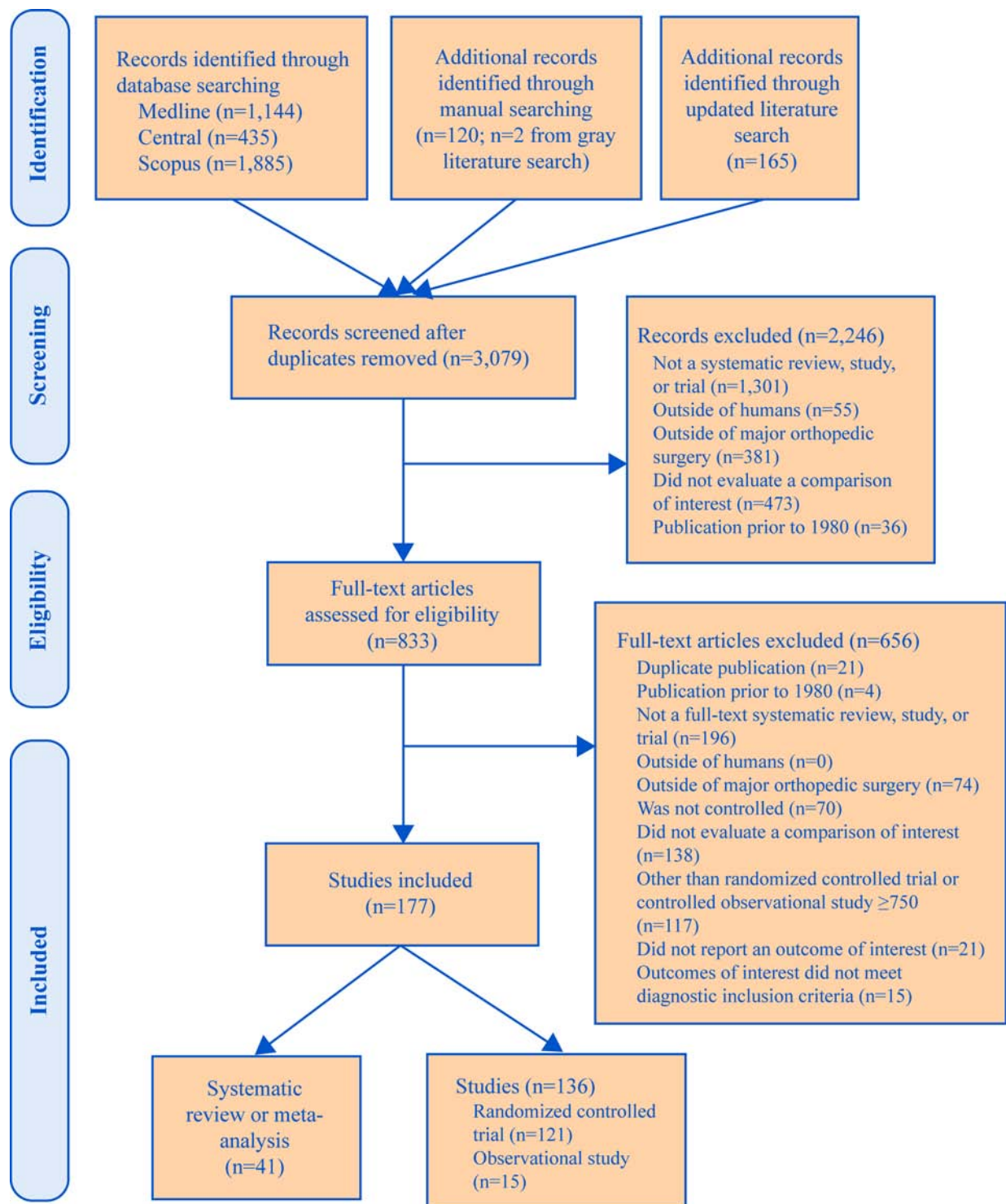


Figure C. PRISMA flow diagram for search two

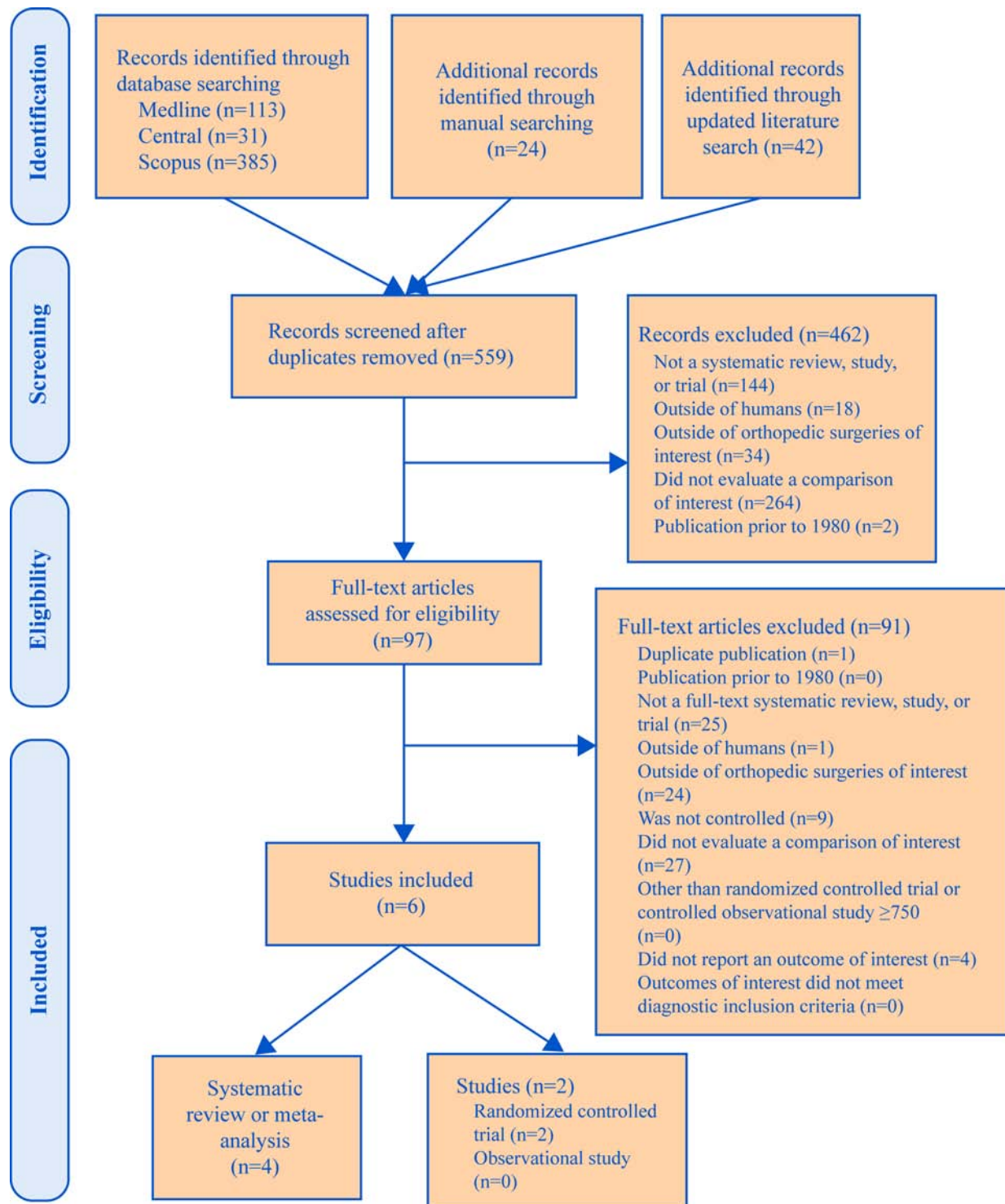


Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 1. Incidence of health outcomes in total hip replacement					
PE	5 RCT	Yes	Pooled incidence of 6% (0.3% to 18%).	L	L
DVT	8 RCT	Yes	Pooled incidence of 39% (25% to 53%).	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 24%.		
Proximal DVT	4 RCT	Yes	Pooled incidence of 32% (14% to 54%).	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 14%.		
Distal DVT	2 RCT	Yes	Pooled incidence of 30% (4% to 68%).	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 17.3%.		
Major bleeding	6 RCT	Yes	Pooled incidence of 1% (0.2% to 2%).	M	L
Minor bleeding	6 RCT	Yes	Pooled incidence of 5% (1% to 13%).	L	M
KQ 1. Incidence of health outcomes in total knee replacement					
PE	2 RCT	Yes	Pooled incidence of 1% (0.07% to 4%).	L	L
	1 OBS	No	The observational study had an incidence of 0.3%.		
DVT	2 RCT	Yes	Pooled incidence of 46% (5% to 91%).	L	L
	1 RCT, 1 OBS	No	One trial not suitable for pooling had an incidence of 68.8% and the observational study had an incidence of 0%.		
Proximal DVT	2 RCT	Yes	Pooled incidence of 17% (1% to 66%).	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 18.8%.		
Distal DVT	2 RCT	Yes	Pooled incidence of 22% (12% to 35%).	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 40.6%.		
Major bleeding	2 RCT	Yes	Pooled incidence of 3% (0.2% to 8%).	L	L
Minor bleeding	2 RCT	Yes	Pooled incidence of 5% (3% to 8%).	M	L
KQ 2. Impact of surgical characteristics on outcomes – general vs. regional anesthesia					
DVT	4 RCT, 2 OBS	No	The majority of trials showed that regional anesthesia was associated with a decrease in the risk of DVT while observational data were conflicting.	L	L
Symptomatic DVT	2 RCT	No	No significant difference.	L	L
Proximal DVT	5 RCT	No	No significant difference.	L	L
KQ 2. Impact of surgical characteristics on outcomes - cemented vs. noncemented arthroplasty					
DVT	2 RCT, 3 OBS	No	No significant difference.	L	L
pDVT	2 RCT	No	No significant difference.	L	L
KQ 2. Impact of patient characteristics on outcomes – congestive heart failure					
Symptomatic objectively confirmed VTE	2 OBS	No	Significantly increases odds.	M	M
KQ 2. Impact of patient characteristics on outcomes – age					
Symptomatic objectively confirmed VTE	2 OBS	No	No significant impact.	L	M
DVT	3 OBS	No	Significantly increased risk.	L	L

Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶ (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Symptomatic objectively confirmed VTE					
LMWH versus FXaI	5 RCTs	Yes	No significant difference, OR 0.70 (0.48 to 1.02).	L	M
LMWH versus VKA	2 RCTs	Yes	No significant difference, OR 1.00 (0.69 to 1.46).	L	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.38 (0.19 to 0.77), NNT 8 to 54.	M	L
KQ 4–8. Major VTE					
Pharmacologic vs. no prophylaxis	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.21 (0.05 to 0.95), NNT 19 to 22.	L	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.26 (0.98 to 1.62).	M	L
KQ 4–8. PE					
Pharmacologic vs. no prophylaxis	12 RCTs	Yes	No significant difference, OR 0.38 (0.13 to 1.07).	L	L
LMWH vs. UFH	10 RCTs	Yes	Significantly decreased odds, OR 0.48 (0.24 to 0.95), NNT 8.	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.18 (0.41 to 3.39).	M	L
LMWH vs. VKA	5 RCTs	Yes	No significant difference, OR 1.11 (0.57 to 2.19).	M	M
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.23 (0.56 to 18.98).	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34).	L	M
Prolonged vs. standard duration prophylaxis	6 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.04 to 0.47), NNT 24 to 232.	H	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80).		
KQ 4–8. Fatal PE					
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.90 (0.38 to 2.13).	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 1.43 (0.08 to 24.82).	L	L
KQ 4–8. Nonfatal PE					
Pharmacologic vs. no prophylaxis	6 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 0.21 (0.04 to 1.30). Observational data were supportive.	L	L
LMWH vs. UFH	10 RCTs	Yes	No significant difference, OR 0.50 (0.25 to 1.00).	L	L
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.68 (0.34 to 1.37).	M	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 0.93 (0.23 to 3.66).	L	L
LMWH vs. VKA	3 RCTs	Yes	No significant difference, OR 1.00 (0.20 to 4.95).	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.27 (0.56 to 18.98).	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34).	L	M
Prolonged vs. standard duration prophylaxis	5 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.03 to 0.54), NNT 58.	M	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06).		

Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶ (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Mortality					
Pharmacologic vs. no prophylaxis	10 RCTs 3 OBS	Yes (RCT)	No significant difference, OR 1.23 (0.54 to 2.78). One observational study supported this finding but another study suggested decrease in number of deaths with prophylaxis.	M	L
LMWH vs. UFH	8 RCTs	Yes	No significant difference, OR 0.39 (0.10 to 1.49).	M	L
LMWH vs. FXaI	5 RCTs 2 OBS	Yes (RCT)	No significant difference, OR 1.08 (0.72 to 1.60). One observational study suggested significantly higher percent of deaths in patients who received LMWH vs. factor Xa inhibitors while the other study suggested no significant difference.	M	L
LMWH vs. DTI	4 RCTs	Yes	No significant difference, RR 0.45 (0.15 to 1.36).	M	L
LMWH vs. VKA	6 RCTs	Yes	No significant difference, OR 0.79 (0.42 to 1.50).	M	M
LMWH vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.31 (0.05 to 1.80).	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 7.13 (0.74 to 68.80).	L	L
KQ 4–8. DVT					
Pharmacologic vs. no prophylaxis	17 RCTs	Yes	Significantly decreased risk, RR: 0.56 (0.47 to 0.68), NNT 3 to 33.	M	L
Antiplatelet vs. mechanical	2 RCTs	Yes	Significantly increased risk, RR 1.63 (1.11 to 2.39), NNH 4 to 27.	M	L
LMWH vs. UFH	13 RCTs	Yes	Significantly decreased risk, RR 0.80 (0.65 to 0.99), NNT 12 to 100.	M	L
	1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17).		
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, RR 1.99 (1.57 to 2.51), NNH 13 to 26.	M	L
LMWH vs. VKA	5 RCTs	Yes	Significantly decreased risk, RR 0.66 (0.55 to 0.79), NNT 6 to 13.	L	M
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 0.90 (0.71 to 1.14).	M	L
UFH vs. DTI	2 RCTs	Yes	Significantly increased risk, RR 2.31 (1.34 to 4.00), NNH 5 to 11.	M	L
VKA vs. mechanical	3 RCTs	Yes	No significant difference, RR 1.45 (0.75 to 2.82).	L	L
Enoxaparin vs. other LMWH	2 RCTs	Yes	No significant difference, RR 1.05 (0.64 to 1.71).	L	L
IPC vs. GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.06 (0.01 to 0.41), NNT 3 to 7.	L	L
Pharmacologic + mechanical vs. pharmacologic	3 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.32 to 0.72), NNT 3 to 67.	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.09 (0.01 to 0.85), NNT 5.		
Prolonged vs. standard duration prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.37 (0.21 to 0.64), NNT 5 to 32.	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97).		

Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶ (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Asymptomatic DVT					
Pharmacologic vs. no prophylaxis	3 RCTs	Yes	Significantly decreased risk, RR 0.52 (0.40 to 0.69), NNT 4 to 6.	M	L
LMWH vs. UFH	2 RCTs	Yes	No significant difference, RR 0.70 (0.43 to 1.16).	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 0.97 (0.85 to 1.10).	M	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.31 to 0.75), NNT 8 to 65.	H	L
KQ 4–8. Symptomatic DVT					
Pharmacologic vs. no prophylaxis	4 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 1.07 (0.25 to 4.52). Observational study data were supportive.	M	L
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.62 (0.22 to 1.75).	L	L
LMWH vs. FXaI	6 RCTs	Yes	No significant difference, OR 0.48 (0.21 to 1.21).	M	M
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 0.98 (0.34 to 2.87).	M	L
LMWH vs. VKA	3 RCTs	Yes	No significant difference, OR 0.87 (0.61 to 1.24).	M	L
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased odds, OR 0.36 (0.16 to 0.81), NNT 27 to 79.	H	M
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87).		
KQ 4–8. Proximal DVT					
Pharmacologic vs. no prophylaxis	12 RCTs	Yes	Significantly decreased risk, RR 0.53 (0.39 to 0.74), NNT 4 to 213.	H	L
LMWH vs. UFH	9 RCTs	Yes	Significantly decreased risk, RR 0.60 (0.38 to 0.93), NNT 14 to 50.	H	L
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, OR 2.19 (1.52 to 3.16), NNH 44 to 122.	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 0.91 (0.40 to 2.11).	L	M
LMWH vs. VKA	6 RCTs	Yes	No significant difference, RR 0.63 (0.39 to 1.00).	L	M
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 0.65 (0.34 to 1.26).	M	L
UFH vs. DTI	2 RCTs	Yes	Significantly increased odds, OR 4.74 (2.99 to 7.49), NNH 11.	M	L
VKA vs. mechanical	3 RCTs	Yes	Significantly decreased risk, RR 0.34 (0.16 to 0.73), NNT 11 to 31.	M	L
Enoxaparin vs. other LMWH	2 RCTs	Yes	No significant difference, RR 1.06 (0.62 to 1.81).	L	L
IPC vs. GCS	2 RCTs	No	No significant difference, one trial showed RR 0.36 (0.13 to 1.00) while the second trial, which compared enoxaparin plus IPC vs. enoxaparin plus GCS, showed OR 0.12 (0.01 to 1.99).	L	M
Pharmacologic + mechanical vs. pharmacologic	3 RCTs	Yes	No significant difference, RR 0.33 (0.09 to 1.22).	L	M
	2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in one trial and RR 0.09 (0.01 to 0.85) in the other trial.		
Pharmacologic + mechanical vs. mechanical	2 RCTs	Yes	No significant difference, RR 0.78 (0.35 to 1.74).	L	L
Prolonged vs. standard duration prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.29 (0.16 to 0.52), NNT 9 to 71.	H	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38).		

Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶ (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Distal DVT					
Pharmacologic vs. no prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.59 (0.42 to 0.82), NNT 8 to 35.	H	L
LMWH vs. UFH	8 RCTs	Yes	No significant difference, RR 0.95 (0.74 to 1.23).	H	L
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, RR 2.02 (1.65 to 2.48), NNH 11 to 33.	H	L
LMWH vs. VKA	2 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.43 to 0.73), NNT 6 to 10.	M	L
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 1.00 (0.77 to 1.29).	M	L
IPC vs. GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.07 (0.01 to 0.54), NNT 3 to 11.	L	M
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons that were pooled to show RR 0.45 (0.16 to 1.26).	M	L
	1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29).		
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	No significant difference, RR 0.39 (0.15 to 1.04).	L	M
KQ 4–8 Major bleeding					
Pharmacologic vs. no prophylaxis	8 RCTs 1 OBS	Yes (RCT)	No significant difference, RR 0.74 (0.36 to 1.51) Observational data were supportive.	M	L
LMWH vs. UFH	7 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.37 to 0.88), NNT 41.	H	L
LMWH vs. FXaI	5 RCTs 2 OBS	Yes (RCT)	Significantly decreased odds, OR 0.65 (0.48 to 0.89), NNT 74 to 145; observational data suggested no significant difference.	M	L
LMWH vs. DTI	4 RCTs	Yes	No significant difference, RR 1.12 (0.80 to 1.57).	M	L
LMWH vs. VKA	7 RCTs	Yes	Significantly increased odds, OR 1.92 (1.27 to 2.91), NNH 57 to 220.	H	M
	1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed an RR 1.51 (0.92 to 2.48) for major bleeding days 0–1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2–8.		
Enoxaparin vs. other LMWH	2 RCT	Yes	No significant difference, RR 1.98 (0.53 to 7.37).	M	L
Prolonged vs. standard duration prophylaxis	5 RCTs	Yes	No significant difference, OR 2.18 (0.73 to 6.51).	L	L
KQ 4–8. Major bleeding leading to reoperation					
LMWH vs. FXaI	4 RCTs	Yes	No significant difference, OR 0.67 (0.28 to 1.61).	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.27 (0.43 to 3.75).	M	L
UFH vs. DTI	2 RCTs	No	No significant difference, one trial had no events and the other trial showed OR 0.51 (0.10 to 2.55).	L	L

Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*⁶ (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Minor bleeding					
Pharmacologic prophylaxis vs. no prophylaxis	6 RCTs	Yes	Significantly increased risk, RR 1.67 (1.18 to 2.38), NNT 30 to 75.	H	M
LMWH vs. UFH	5 RCTs	Yes	No significant difference, RR 0.90 (0.63 to 1.28).	M	L
LMWH vs. FXaI	2 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.35 to 0.94), NNT 31 to 60.	L	
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR: 1.07 (0.89 to 1.29).	M	L
LMWH vs. VKA	7 RCTs	Yes	Significantly increased risk, RR 1.23 (1.06 to 1.43), NNH 18 to 218.	M	M
	1 RCT (2 comp)	Yes	One trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0–1 and a RR 0.87 (0.37 to 2.06) on days 2–8.		
VKA vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.80 (0.26 to 2.41).	L	L
Prolonged vs. standard duration prophylaxis	3 RCTs	Yes	Significantly increased odds, OR 2.44 (1.41 to 4.20), NNH 11 to 118.	H	M
KQ 4–8. Surgical site bleeding					
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.92 (0.46 to 1.82).	L	L
LMWH vs. VKA	2 RCT	Yes	Significantly increased odds OR 2.63 (1.31 to 5.28), NNH 23 to 64.	L	L
Enoxaparin vs. other LMWH	2 RCT	Yes	No significant difference, RR 1.35 (0.30 to 5.97).	L	L
KQ 4–8. Bleeding leading to transfusion					
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 1.00 (0.59 to 1.69).	H	L
KQ 4–8. HIT					
LMWH vs. UFH	3 RCTs	Yes	Significantly decreased odds, OR 0.12 (0.03 to 0.43), NNT 34 to 202.	M	L
KQ 4–8. Readmission					
LMWH vs. UFH	2 RCT	Yes	No significant difference, RR 0.82 (0.20 to 3.38).	L	L
LMWH vs. mechanical	2 RCT	Yes	No significant difference, OR 0.83 (0.22 to 3.11).	L	L
Prolonged vs. standard duration prophylaxis	1 RCT (2 comp)	Yes	No significant difference, RR 0.29 (0.06 to 1.34).	L	L

AOE = applicability of evidence; DTI = direct thrombin inhibitor; DVT = deep vein thrombosis; FXaI = factor Xa inhibitor; H = high; IPC = intermittent pneumatic compression; KQ = Key Question; L = low; LMWH = low molecular weight heparin; M = moderate; NNH = number needed to harm; NNT = number needed to treat; OBS = observational; OR = Peto's Odds Ratio; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; UFH = unfractionated heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism

*Denotes that all base case analyses with at least one randomized controlled trial or one controlled observational study and a strength of evidence of low, moderate, or high evaluating the given outcome are represented in this table.

Discussion

In the comparative effectiveness review of patients having major orthopedic surgery, DVT is still common in the absence of prophylaxis and PE and major bleeding outcomes also occur, although at lower rates. We do not have adequate data looking at the association between specific surgical or patient factors and the occurrence of health outcomes of interest. The impact of the intermediate outcome of DVT on final health outcomes such as PE cannot be determined with confidence. It is difficult to discriminate between DVT being causative for, or colinear with,

the occurrence of PE given the available literature. The comparative balance of benefits and harms is favorable for providing pharmacologic prophylaxis and possibly for providing mechanical prophylaxis as well and providing longer term prophylaxis (28 days or longer) versus using only short term prophylaxis (7 to 10 days).

While there are advantages of LMWHs over UFH in terms of the balance of benefits and harms, the comparative balance for LMWHs versus other drug classes is harder to determine because there is a tradeoff between benefits and harms (better efficacy vs. VKAs but higher bleeding; worse efficacy vs. factor Xa inhibitors but lower bleeding). Injectable UFH is likely inferior to factor Xa inhibitors in the balance of benefits and harms as well. When we evaluated intraclass comparisons, the literature base was insufficient overall to determine the balance of benefits and harms for one LMWH versus another or for one mechanical modality over another. We cannot determine if the balance of benefits and harms is favorable for combining pharmacologic and mechanical modalities of prophylaxis together versus simply using one modality alone, due to the insufficient amount of data.

There are numerous limitations to the current literature base which aid in identifying priorities for future research needs. Although major orthopedic surgery is inclusive of total hip or knee replacement surgery and hip fracture surgery, the vast majority of literature evaluated hip or knee replacement surgery with very little evaluation of hip fracture surgery. When we assessed orthopedic surgeries other than THR, TKR, and HFS, the literature base was inadequate to determine benefits or harms, and therefore, studies comparing prophylactic strategies versus no prophylaxis are needed to discern if prophylaxis is needed in nonmajor orthopedic surgeries. Although trials were designed to report events that occurred during the period of followup, many times no events occurred in evaluating fatal pulmonary embolism, pulmonary embolism, mortality due to bleeding, major bleeding, major bleeding leading to reoperation, and bleeding leading to transfusion. KQs 4, 5, and 8 were most affected by this, and although in the majority of cases, trials were adequately designed to detect outcomes, the followup period was likely inadequate to capture the occurrence of events. Additionally, these outcomes were not commonly primary outcomes of the trials and therefore were underpowered to detect differences, which were not overcome by pooling since the events were rare.

While we found that there is a real risk of developing DVT, PE, and major bleeding with major orthopedic surgery, there are inadequate data to say whether DVT causes PE. We were not even able to determine that DVT is an independent predictor of PE which would be the next logical step to be assessed in a large observational study. Similarly, determining the impact of symptomatic and asymptomatic DVT on patient perceived quality of life could help determine the importance of this intermediate outcome, although no literature was found evaluating health-related quality of life. LMWHs have a better balance of benefits and harms compared with UFH in major orthopedic surgery, but in general, whether one agent within the class should be used versus another is not clearly determined. Future direct comparative trials are needed between classes of drugs, but funding these trials could be difficult to conduct since aspirin, warfarin, and UFH are generically available. The large number of mechanical prophylactic devices available also makes it difficult to conduct a trial with strong applicability to all devices. Harms such as bleeding leading to infection, bleeding leading to transfusion, readmission, and reoperation were rarely reported. In all cases, harms need to be determined because as we have suggested, in many comparisons between classes, there is a tradeoff between increased efficacy and increased bleeding. Future studies assessing the utility of dual prophylaxis versus single modality therapy are also needed.

Addendum

After this report was updated, the Food and Drug Administration approved an oral direct factor Xa inhibitor, rivaroxaban, for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing knee or hip replacement surgery. Four phase 3 trials have been completed at this time.⁶ Since this drug did not carry an FDA-approved indication until recently, rivaroxaban did not meet the inclusion criteria and was not included in this report. We find these trials relevant since they provide new information for an additional between class comparison (oral direct factor Xa inhibitor versus injectable low molecular weight heparin) in KQ 5. The drug has been studied in both total hip and knee replacement surgical populations. The main findings of the four trials and the outcomes reported in these trials that are consistent with our methodology are described in detail within the full report.

Glossary

Confidence Interval (CI): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.

Deep Vein Thrombosis (DVT): A blood clot occurring in a leg vein and verified with Doppler ultrasound or venography. Proximal deep vein thrombosis was defined as blood clot occurring in either popliteal, femoral, or any deep veins of the pelvis. Distal vein thrombosis was defined as blood clot occurring distal to the popliteal vein in the calf veins of the leg. When both bilateral and unilateral clots data were available, unilateral clots data were used for the analysis.

DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.

Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.

Hip Fracture Surgery (HFS): The surgical procedure to treat hip fracture.

I²: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

Major Orthopedic Surgery: Total hip arthroplasty, total knee arthroplasty, hip fracture surgery.

Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.

Other Orthopedic Surgery: Knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or disectomy all of the lumbar region).

Peto's Odds Ratio (OR): An odds ratio is the ratio of an event occurring in an exposed group to an event occurring in the nonexposed group in a given population. A ratio of 1 indicates no difference in the odds between the two groups. Peto's odds ratios are used to compare two groups when the number of events is rare.

Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.

Pulmonary Embolism (PE): A blood clot in the vasculature of the lung. In order to have a pulmonary embolism in our review, it needed to be verified with spiral computed tomography angiography or ventilation/perfusion scan with either Prospective Investigation of Pulmonary

Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for pulmonary embolism.

Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a nonexposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.

Sensitivity Analyses: A “what if” analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.

Standard Deviations (SDs): A measure of the variability of a dataset. For a simple dataset with numbers, can be calculated using the following formula: $\sigma = ((\sum(x-x_m))^2/N)^{0.5}$ where σ is standard deviation, x_m is the average, $\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x , N is the total number of values.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis.

Total Hip Arthroplasty (THR): The surgical replacement of the hip.

Total Knee Arthroplasty (TKA): The surgical replacement of the knee.

Venous Thromboembolism (VTE): The occurrence of either a deep vein thrombosis or pulmonary embolism.

References

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:381S-453S. PMID: 18574271
2. American Academy of Orthopaedic Surgeons. Clinical guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. www.guideline.gov/content.aspx?id=10850.
3. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2011. Chapters available at: www.effectivehealthcare.ahrq.gov.
4. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77. PMID: 16596572
5. Owens D, Lohr K, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions: AHRQ and the effective health care program. *J Clin Epidemiol* 2010;63:513-23. PMID: 19595577
6. Sobieraj DM, Coleman CI, Tongbram V, Lee S, Colby J, Chen WT, Mekanji SS, Ashaye A, Kluger J, White CM. Venous Thromboembolism Prophylaxis in Orthopedic Surgery. Comparative Effectiveness Review No. 49. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 12-EHC020-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Introduction

Background

Major orthopedic surgery (total hip replacement, total knee replacement or hip fracture surgery) carries a high risk of venous thromboembolism. Pulmonary embolism following orthopedic surgery is reported to be rare.¹ However, without prophylaxis, historical data suggest that hospital acquired deep venous thrombosis has been estimated to occur in 40 to 60 percent of cases in the 7 to 14 days following surgery compared with 10 to 40 percent among medical or general surgical patients.² While asymptomatic deep vein thrombosis is identified more frequently than symptomatic deep vein thrombosis in clinical trials due to routine screening, there is disagreement as to the clinical relevance of asymptomatic cases.^{3,4} While certain patient characteristics (i.e. age, immobility, comorbidities) have been suggested to increase the risk of venous thromboembolism regardless of the clinical setting, major orthopedic surgery contributes additional factors such as use of general anesthesia which may prolong immobility and surgical involvement of the femoral vein.^{5,6}

A variety of strategies to prevent venous thromboembolism are available and with routine use, the rate of symptomatic venous thromboembolism in patients within 3 months of surgery is 1.3 to 10 percent.² The main limitation of pharmacologic venous thromboembolism prophylaxis is the risk of bleeding. Based on historical data major bleeding following total hip replacement and total knee replacement is estimated to be 1 to 3 percent.¹ Determining the incidence of major bleeding with pharmacologic thromboprophylaxis is complicated by the variability in the definitions used in published literature and paucity of data in control patients. Additionally, complications such as postoperative bleeding and hematoma formation are considered risk factors for the development of early onset prosthetic joint infections.^{7,8} Reoperation is frequently required for debridement with or without removal of the infected prosthesis. Following removal of an infected prosthesis and extended intravenous antibiotic treatment further surgery may be required to either implant a new prosthesis or perform an arthrodesis of the joint.

There are many unknowns that need to be explored in a comparative effectiveness review. In contemporary practice, the risk of venous thromboembolism, pulmonary embolism, and deep vein thrombosis, and the causal link between deep vein thrombosis and pulmonary embolism has not been well established. Previous observations of the incidence of pulmonary embolism in patients who have undergone orthopedic surgery with confirmed deep vein thrombosis suggests that pulmonary embolism and deep vein thrombosis are related disorders.⁹ However, whether the presence of deep vein thrombosis affects the risk of pulmonary embolism and to what degree if so remains unclear in the literature.^{3,4} Widespread use of anticoagulants to treat venous thromboembolism for many decades along with the evolution of diagnostic strategies have limited the availability of literature regarding the natural history of venous thromboembolism.¹⁰ In addition to major orthopedic surgery, there are a variety of other orthopedic surgeries in which the impact of venous thromboembolic prophylaxis has not been well evaluated. These orthopedic surgeries of interest include knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery. While prophylactic strategies may decrease the risk of venous thromboembolism, pulmonary embolism, and deep vein thrombosis, the magnitude of benefit in contemporary practice using rigorous definitions of endpoints and the impact of duration of prophylaxis on outcomes is not well delineated. Whether dual prophylactic strategies are superior to a single modality is not well defined. In addition, in order to determine comparative

effectiveness, both the benefits and harms need to be appreciated. Finally, several previous meta-analyses and guidelines allowed the use of medications or devices that are not available for use in the United States reducing their applicability.

Objective

To perform a comparative effectiveness review examining the benefits and harms associated with venous thromboembolism prophylaxis in patients undergoing major orthopedic surgery, knee arthroscopy, or other orthopedic surgeries including surgical repair of a lower extremity injury distal to the hip and elective spine surgery. The analytic framework is presented in Figure 1.

Key Questions

Key Question 1. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of venous thromboembolism and bleeding outcomes in contemporary practice?

Key Question 2. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what patient, surgical or postsurgical characteristics predict or differentiate patient risk of venous thromboembolism and bleeding outcomes in contemporary practice?

Key Question 3. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?

Key Question 4. In patients who had major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism-related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep vein thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists) or any external mechanical intervention within the defined classes (graduated compression stockings, intermittent pneumatic compression devices, or venous foot pumps)]?

Key Question 5. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep

vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists, and mechanical interventions.

Key Question 6. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual agents within classes (injectable low molecular weight heparin or mechanical) on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Question 7. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Question 8. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Question 9. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents,

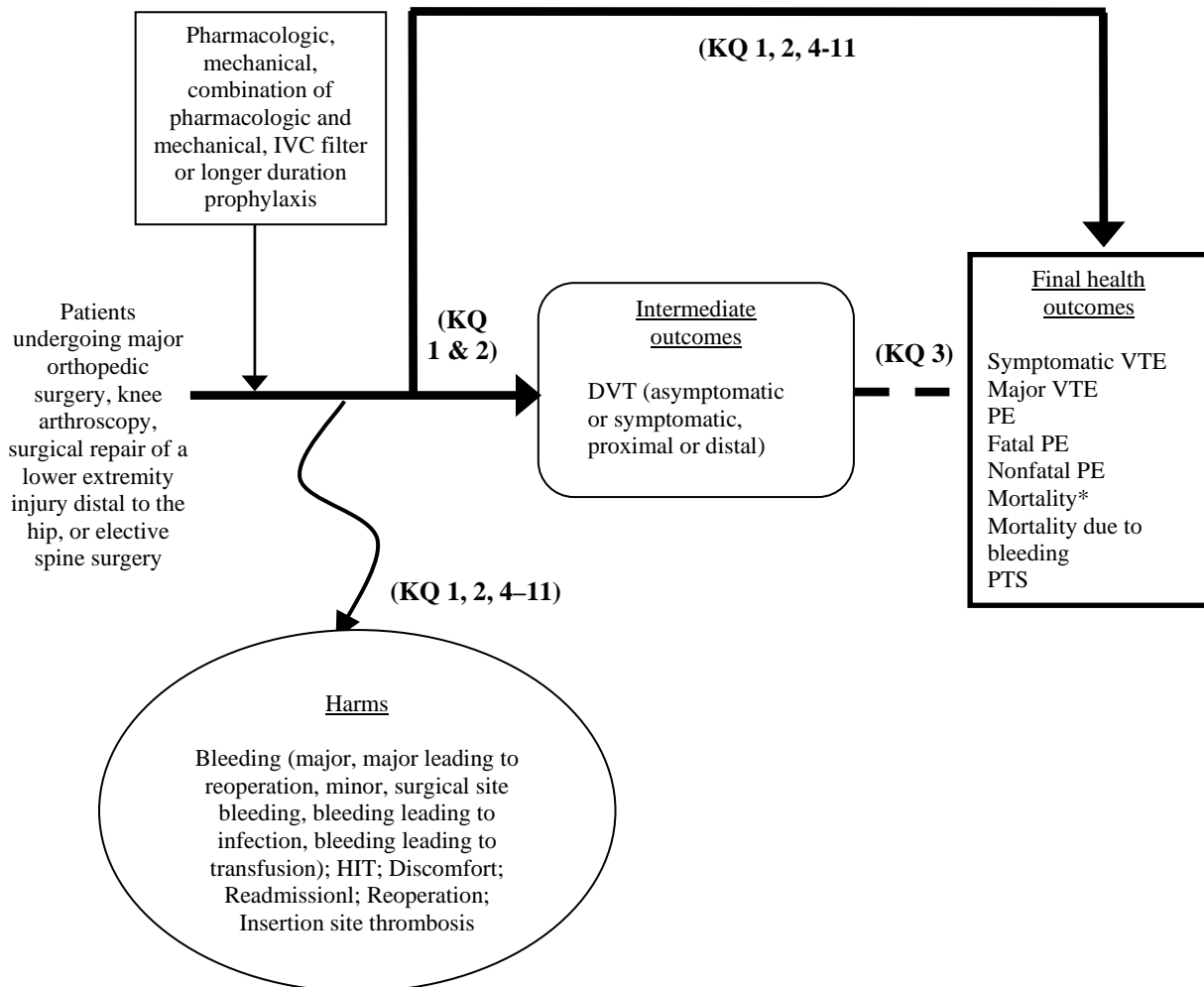
what is the relative impact of prophylactic inferior vena cava filter placement compared with any external mechanical intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, reoperation or IVC filter placement-associated insertion site thrombosis?

Key Question 10. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Question 11. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (low molecular weight heparin agents, injectable unfractionated heparin, injectable factor Xa inhibitors, injectable direct thrombin inhibitors) compared with mechanical interventions on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Analytic Framework

Figure 1. Analytic framework for the comparative effectiveness of venous thromboembolism prophylaxis in orthopedic surgery



DVT = deep vein thrombosis; HIT = heparin induced thrombocytopenia; PE = pulmonary embolism; PTS = post thrombotic syndrome; VTE = venous thromboembolism

*Mortality is all-cause mortality.

Methods

Input From Stakeholders

The Evidence-based Practice Center drafted a topic refinement document with proposed Key Questions after consult with Key Informants. Our Key Informants included eight physicians: three provided the orthopedic surgeon's perspective one of which was a local expert, one provided a local pulmonologist's perspective, two provided expertise in methodology/guideline development, one provided a hematologist's perspective, and one provided expertise in health policy. There was equal representation from both the American College of Chest Physicians and the American Academy of Orthopedic Surgeons (three members each). Our Key Informants did not have financial or other declared conflicts. The public was invited to comment on the topic refinement document and Key Questions. After reviewing the public commentary, responses to public commentary, proposed revisions to the Key Questions, and a preliminary protocol was generated and reviewed with the Technical Expert Panel. The aforementioned Key Informants constituted our Technical Expert Panel and provided feedback on the feasibility and importance of our approach and provided their unique insight. Again, no conflict of interest was identified. The draft CER report underwent peer review and public commentary and revisions were made before finalizing the report.

Searching for the Evidence

Two independent investigators conducted systematic literature searches in July 2010 of Medline, The Cochrane Central Register of Controlled Trials, and Scopus from 1980 to the July 2010. The restriction of 1980 was used to reflect contemporary practice. Language restrictions were not imposed and professional translation services were utilized when necessary. Two separate searches of these databases were conducted and the complete search strategies are included in Appendix A. The first search was used to identify studies which evaluated pharmacologic, mechanical, or inferior vena cava filter methods of thromboprophylaxis in patients undergoing major orthopedic surgery, described the association between patient, surgical, or postsurgical characteristics and venous thromboembolism or bleeding, or described the association between intermediate and final health outcomes to answer Key Questions 1 through 9. The second search was used to identify studies which evaluated pharmacologic or mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip or elective spine surgery to answer Key Questions 10 and 11. A manual search of references of clinical trials, meta-analyses, and systematic reviews was conducted. A grey literature search of regulatory documents, abstracts, and ongoing clinical trials was conducted by the Scientific Resource Center and reviewed by two independent investigators for inclusion into our literature base by applying the same a priori defined inclusion criteria defined below. The literature search was updated in May 2011 using the same search strategy.

Inclusion and Exclusion Criteria

Two independent investigators assessed studies for inclusion in a parallel manner based on a priori defined criteria. In evaluating all Key Questions, randomized controlled trials of any size or controlled observational trials (case-controlled or cohort studies) enrolling ≥ 750 patients were

included if they explicitly reported the use of imaging studies to confirm venous thromboembolic events (Doppler ultrasound or venography for deep vein thrombosis and spiral computed tomography angiography or ventilation/perfusion scan with either Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for pulmonary embolism.^{11,12} Observational studies that enrolled <750 subjects were excluded because numerous RCTs in this literature base enroll over 500 participants, with the most contemporary trials enrolling over 1,000 participants. Therefore observational studies would need to be of larger size to provide additional valuable information on outcomes of interest and applicability. Studies were included if the pharmacologic thromboprophylaxis agent to which patients were randomized had Food and Drug Administration approval for any indication and mechanical thromboprophylactic devices to which patients were randomized were available for use in the United States.

Additional inclusion criteria for the evaluation of Key Question 1 were (1) studies which included only patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) or reported separate results for these major orthopedic surgeries; (2) studies which compared pharmacologic or mechanical methods of thromboprophylaxis with placebo or control without off protocol use of pharmacologic or mechanical methods of prophylaxis or studies included in other Key Questions which included a placebo or control arm without off protocol use of pharmacologic or mechanical methods of prophylaxis; and (3) reported data on at least one prespecified venous thromboembolic or bleeding outcome.

Additional inclusion criteria for the evaluation of Key Question 2 were (1) studies which included only patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) or reported separate results for these major orthopedic surgeries; and (2) described the association of patient, surgical or postsurgical characteristics and prespecified venous thromboembolic or bleeding outcomes. Studies were included only if adjustments were made for confounding factors (multivariable regression, randomization, or propensity score matching).

Additional inclusion criteria for the evaluation of Key Question 3 were (1) studies which included only patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) or reported separate results for these major orthopedic surgeries and (2) studies which reported data on both pulmonary embolism (asymptomatic or symptomatic) and deep vein thrombosis (asymptomatic or symptomatic). For this Key Question, due to the paucity of data, trials and studies were allowed that did not follow the strict diagnostic inclusion criteria previously identified. For transparency, diagnostic criteria were explained for each study included in the results of this Key Question.

For Key Questions 4 through 9, studies were included if the study reported data on at least one prespecified outcome of interest and included only patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) or reported separate results for these major orthopedic surgeries. Additionally, for Key Question 4 only studies which compared pharmacologic or mechanical prophylaxis with placebo or control without the use of off protocol prophylaxis (with the exception of elastic stockings) were included. For Key Question 5, only studies which randomized patients into one pharmacologic or mechanical intervention versus another single intervention were included. For Key Question 7, only studies which randomized patients to a combination of pharmacologic plus mechanical prophylaxis versus one of the interventions alone were included.

Additional inclusion criteria for the evaluation of Key Questions 10 and 11 were (1) studies which included only patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or discectomy all of the lumbar region) or reported separate results for these orthopedic surgeries; (2) compared pharmacologic or mechanical methods of thromboprophylaxis versus control or compared injectable antithrombotic agents (low molecular weight heparin, unfractionated heparin, factor Xa inhibitors, direct thrombin inhibitors) to mechanical interventions; (3) studies which reported data on at least one prespecified outcome of interest.

Data Extraction and Data Management

Two reviewers used a standardized data extraction tool to independently extract study data with disagreements resolved through discussion. (Appendix B) The following data were collected from each trial when applicable: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population (inclusion and exclusion criteria, geographic location, thromboprophylaxis intervention, length of study, duration of patient followup), patient baseline, surgical and postsurgical characteristics (including those which may modify risk of venous thromboembolism or bleeding), thromboprophylaxis regimen (name, strength, dose, frequency, route of administration and duration of therapy for pharmacologic interventions; name, frequency of use, and adherence for mechanical interventions), mobilization status of the patients, use of concurrent standard medical therapies, data needed to assess intermediate and final health outcomes and adverse events, outcome definition, diagnostic test used to confirm outcome of interest, and data reported for subgroups of interest (age, gender, ethnicity). Authors were contacted for clarification or to provide additional data when necessary. If a pharmacologic method of prophylaxis was included in this report on the premise of Food and Drug Administration approval for an indication other than venous thromboembolism prophylaxis, data were extracted for the regimen which most closely resembled that from phase 3 clinical trials.

Assessment of Methodological Quality of Individual Studies

Validity assessment was performed using the recommendations in the Methods Guide for Comparative Effectiveness Review. Each study was assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals (percent followup) and potential conflict of interest. Additionally, randomized controlled trials were assessed for randomization technique and allocation concealment. Observational studies were assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were given an overall score of good, fair, or poor in Table 1.

Table 1. Summary of rating of quality of individual studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; and clear reporting of dropouts.
Fair	These studies are susceptible to some bias, but it is not sufficient to invalidate results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information, or discrepancies in reporting.

Data Synthesis

Key Questions 1 and 2 explore the baseline postoperative risk of venous thromboembolism and bleeding and the patient, surgical, or postsurgical characteristics that predict or differentiate the risk of venous thromboembolism or bleeding in major orthopedic surgery. These questions were answered with studies reflecting contemporary clinical practice (literature published in or after 1980). In Key Question 1, the baseline postoperative risk of venous thromboembolic outcomes was estimated for each of the major orthopedic surgeries separately. Incidences for each outcome were extracted from placebo or control arms of trials and pooled for each major orthopedic surgery. If only one arm was available, the raw incidence of the outcome from the trial was reported. The same was done for bleeding outcomes although arms which allowed the off protocol use of elastic stockings were also include. In Key Question 2, the patient, surgical, and postsurgical characteristics which were analyzed within trials or studies for their impact on venous thromboembolism or bleeding risk were reported and summarized qualitatively.

Key Question 3 explores the link between intermediate and final health outcomes and was qualitatively reported and summarized. From randomized controlled trials, the event rates of both asymptomatic and symptomatic pulmonary embolism and deep vein thrombosis from in patients undergoing major orthopedic surgery with use of the pharmacologic methods of venous thromboembolism prophylaxis were reported. Additionally, results of observational studies which reported predictors of pulmonary embolism were included qualitatively. We would have included any human trial or study that provided insight into the relationship between deep venous thrombosis and pulmonary embolism.

The remaining Key Questions 4 through 11 explore the impact of thromboprophylaxis on final health outcomes, intermediate outcomes, and adverse effects. We qualitatively examined data from all identified studies. The base case analysis for each Key Question was in major orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). For each outcome, we conducted separate analyses of studies comparing each individual thromboprophylactic intervention with placebo or control and studies in which different thromboprophylactic interventions were compared with each other. Key Questions 5 through 9 and 11 explore direct comparisons between or within specified classes and therefore only direct comparison trials were used in their quantitative analysis. In Key Question 6, within class comparisons are made for low molecular weight heparin agents and mechanical prophylaxis modalities. Data from trials will be pooled for like agents when possible and compared with other agents in the class (i.e. one low-molecular weight heparin agent versus others). In Key

Questions 10 and 11, trials pertaining to each orthopedic surgery category (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery) were discussed separately due to the paucity of data that met inclusion criteria.

We conducted meta-analyses when two or more trials adequate for pooling were available for any outcome. Randomized controlled trials were pooled but data from observational studies were not. For dichotomous outcomes, weighted averages are reported as relative risks or Peto's odds ratio with associated 95 percent confidence intervals. Peto's odds ratio was chosen over relative risk when the control event rate was exceptionally low (less than 5 percent) and the number of subjects randomized in each group of a trial was similar in the majority of trials within the given analysis.¹³ As heterogeneity between included studies was expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating relative risks and 95 percent confidence intervals.¹⁴ Trials with zero events in both arms were excluded from analyses as they do not provide information on the direction or magnitude of the effect.¹⁵ In the event that there was more than one method of thromboprophylaxis being compared with another method of thromboprophylaxis (i.e. low molecular weight heparin versus low molecular weight heparin plus compression stockings versus compression stockings), each method of thromboprophylaxis was compared individually against the other (as a separate trial) by dividing the control group equally between the comparisons.¹⁴ The number needed to treat (NNT) or number needed to harm (NNH) was calculated for statistically significant results of the base case analysis for Key Questions 4 through 11. To account for the variability in baseline risk that may be seen in clinical practice, the range of control event rates in the individual trials for a pooled analysis was considered when calculating the NNT and NNH. An equation which utilizes the control event rate and the relative effect estimate was applied to the lowest and highest control event rate in the range and then the NNT and NNH were reported as a range. When a trial with no events was included in the pooled analysis, a range could not be calculated for the NNT or NNH and instead a single value is presented.

Statistical heterogeneity was addressed using the I^2 statistic (which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity). While categorization of values for I^2 may not be appropriate in all situations, I^2 values of less than 50 percent and greater than 50 percent have been regarded as representative of lower and higher levels of statistical heterogeneity, respectively. Egger's weighted regression statistics was used to assess for the presence of publication bias. Statistical analyses were performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 was considered statistically significant for all analyses.

Subgroup and sensitivity analyses were conducted to assess the effect of heterogeneity (both clinical and methodological) on our meta-analysis' conclusions. For Key Questions 1 through 9, in the events that the base case analysis for a Key Question was in major orthopedic surgery (total hip or knee replacement or hip fracture surgery) subgroup analyses in total hip replacement, total knee replacement and hip fracture surgery were conducted. Additional subgroup analyses included publication year (prior to 2001 versus 2001-present, with present defined as May 2011), gender, ethnicity and age. In Key Question 4, subgroup analysis was conducted on trials which compared an active intervention with placebo or control without off protocol use of elastic stockings, which is referred to as "true placebo" in this report.

Grading the Strength of the Evidence

We used the Evidence-based Practice Center Grading of Recommendations Assessment, Development guide to assess the strength of evidence.¹⁶ This system uses four required domains; risk of bias, consistency, directness, and precision. Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. For study design, whether the study was a randomized controlled trial or an observational study was recorded. Studies were ranked as having no limitations, serious limitations, or very serious limitations. Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We assessed whether or not the effect sizes were on the same side of unity, whether the range of effect sizes was narrow, and the degree of statistical heterogeneity in evaluating consistency. We ranked this domain as no inconsistency, serious inconsistency, and very serious inconsistency. When only a single study is included, consistency cannot be judged. Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We ranked this domain as no indirectness, serious indirectness, and very serious indirectness. Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we evaluated the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion. Additional optional domains were not determined to be necessary and were not utilized.

All assessments were made by two investigators with disagreements resolved through discussion. The evidence pertaining to each Key Question was classified into four broad categories; high, moderate, low or insufficient. In Table 2 we describe in more detail the features that determined the strength of evidence for the different outcomes evaluated in this report.

Table 2. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Evaluating the Applicability of the Evidence

Effectiveness studies met five of the following seven criteria: enrolled an orthopedic surgery population, used less stringent eligibility criteria, assessed final health outcomes, allowed for adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention to treat analysis.¹⁷ Studies which met less than five criteria were classified as efficacy trials and were deemed to have less applicability. In addition, factors identified in Table 3 were important when determining applicability and were extracted into evidence tables for every study. Given these inputs, the applicability of each study

was determined as was the applicability for the body of evidence for the base case analysis of each comparison within a Key Question.

Table 3. Applicability considerations and data extracted

Feature	Condition That Limits Applicability	Features To Be Extracted Into Evidence Table
Population	Differences between patients in study and the community	Eligibility criteria, demographics
Population	Events rates markedly different than in community	Event rates in treatment and control groups
Intervention	Treatment not reflective of current practice	Complete regimen of thromboprophylactic intervention (pharmacologic, mechanical, or IVC filter)
Comparator	Use of substandard alternative therapy	Type of comparator
Outcomes	Surrogate endpoints, brief followup periods, improper definitions for outcomes, composite endpoints	Outcomes (benefits and harms) and how they were defined and diagnosed
Settings	Settings where standards of care differ markedly from setting of interest	Clinical Setting and geographic setting

Results

Results of the Literature Search

Two literature searches were conducted as previously described in the methods. The first search was used to identify literature to answer Key Questions 1 through 9. Upon conducting this literature search, we retrieved 3,464 unique citations from the database search, 120 citations from a manual review of the literature, and two citations added manually from the gray literature search conducted by the Scientific Resource Center. Upon updating the literature search in May 2011, a total of 165 citations were retrieved. After duplicate citations were removed, 3,079 citations remained. A total of 2,426 citations were excluded at the title and abstract level while 656 citations were excluded at the full text level. A total of 177 articles were found to match our inclusion criteria. A summary of search results is presented in Figure 2. All citations excluded at the full text level are listed in Appendix C along with the reason for exclusion.

Of the 177 articles included in search one, 121 articles represented 98 unique randomized controlled trials (n=44,469).^{18-27,27-135} Fifteen articles represented 14 unique controlled observational studies (n=480,241).¹³⁶⁻¹⁵⁰ Further details regarding the included trials and studies are provided per Key Question for those included in answering the Key Question. The study characteristics and quality of randomized controlled trials and observational studies are included in Appendix D and the baseline and procedural characteristics of enrolled patients in these trials and studies are in Appendix E. An overview of the results for Key Questions 1 through 10 can be found in Table 4. Evaluations for Key Questions 9 through 11 had insufficient strength of evidence and are not included. Evidence tables for final and intermediate health outcomes and harms are presented in Appendix F.

Forty-one articles represented 39 unique systematic reviews or meta-analyses.¹⁵¹⁻¹⁹⁰ Of these, five meta-analyses were deemed relevant for comparison to the results of Key Question 1 and are described in Table 5.^{153,159,164,169,171} Nineteen meta-analyses were deemed relevant for comparison to other Key Questions and are described in Table 6. The remaining systematic reviews and meta-analyses were used to manually search for additional literature which met our inclusion criteria.

The second literature search was used to identify literature to answer Key Questions 10 through 11. Upon conducting this literature search, we retrieved 529 unique citations from the database search and 24 citations from a manual review of the literature. Upon updating the literature search in May 2011, a total of 42 citations were retrieved. After removal of duplicate citations, 559 citations remained. A total of 462 citations were excluded at the title and abstract level while 91 citations were excluded at the full text level. A total of six articles met our inclusion criteria. A summary of search results is presented in Figure 3. All citations excluded at the full text level are listed in Appendix C along with the reason for exclusion. Of the six articles included in search two, two articles represented two unique randomized controlled trials (n=235).^{191,192} The trial characteristics and quality of the trials as well as the baseline and procedural characteristic of enrolled patients can be found in Appendixes D and E. Four articles represented three unique meta-analyses which were used to manually search for additional literature which met our inclusion criteria as well as to summarize findings pertinent to Key Questions 10 and 11.¹⁹³⁻¹⁹⁶

Figure 2. PRISMA flow diagram for search one

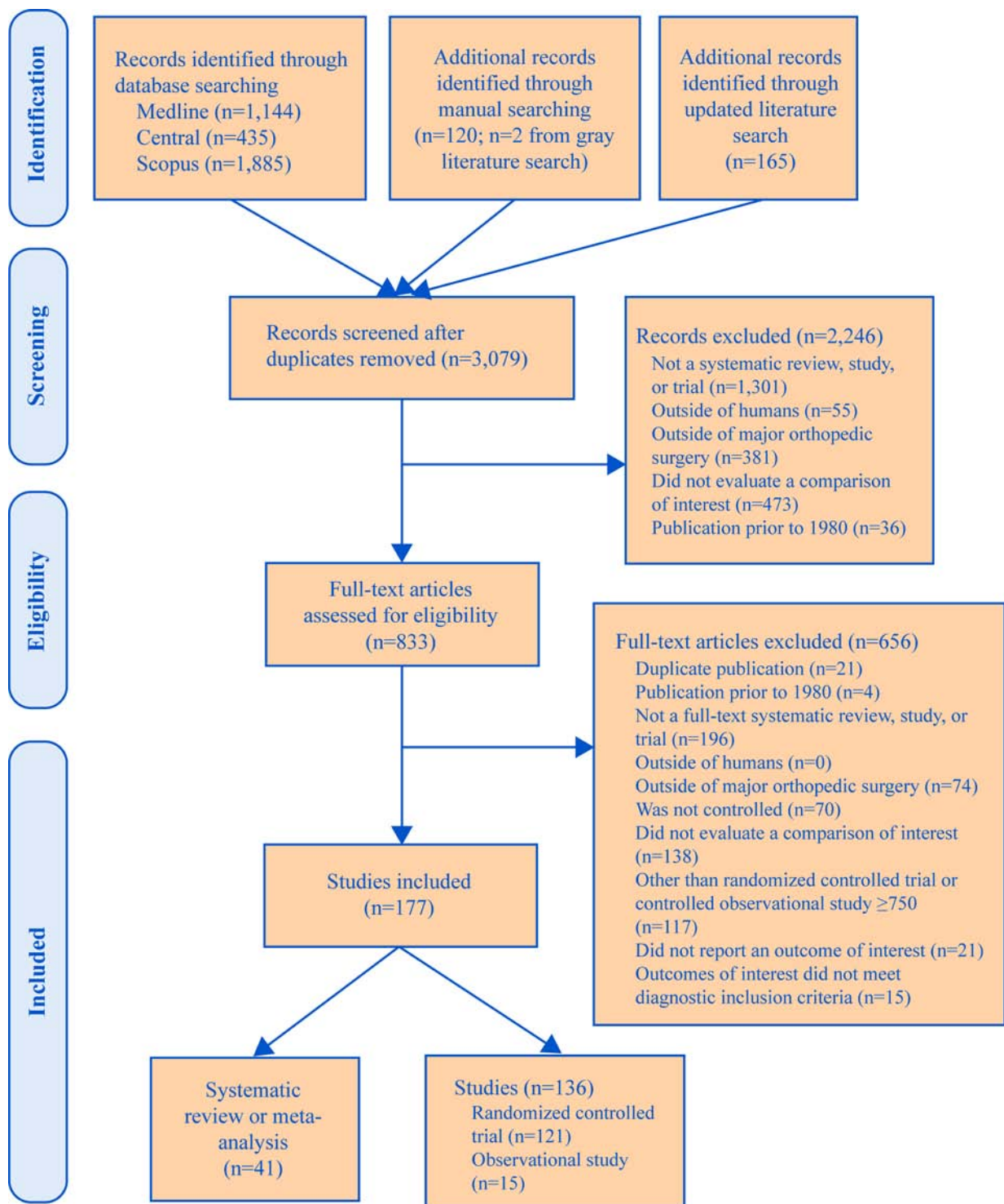


Figure 3. PRISMA flow diagram for search two

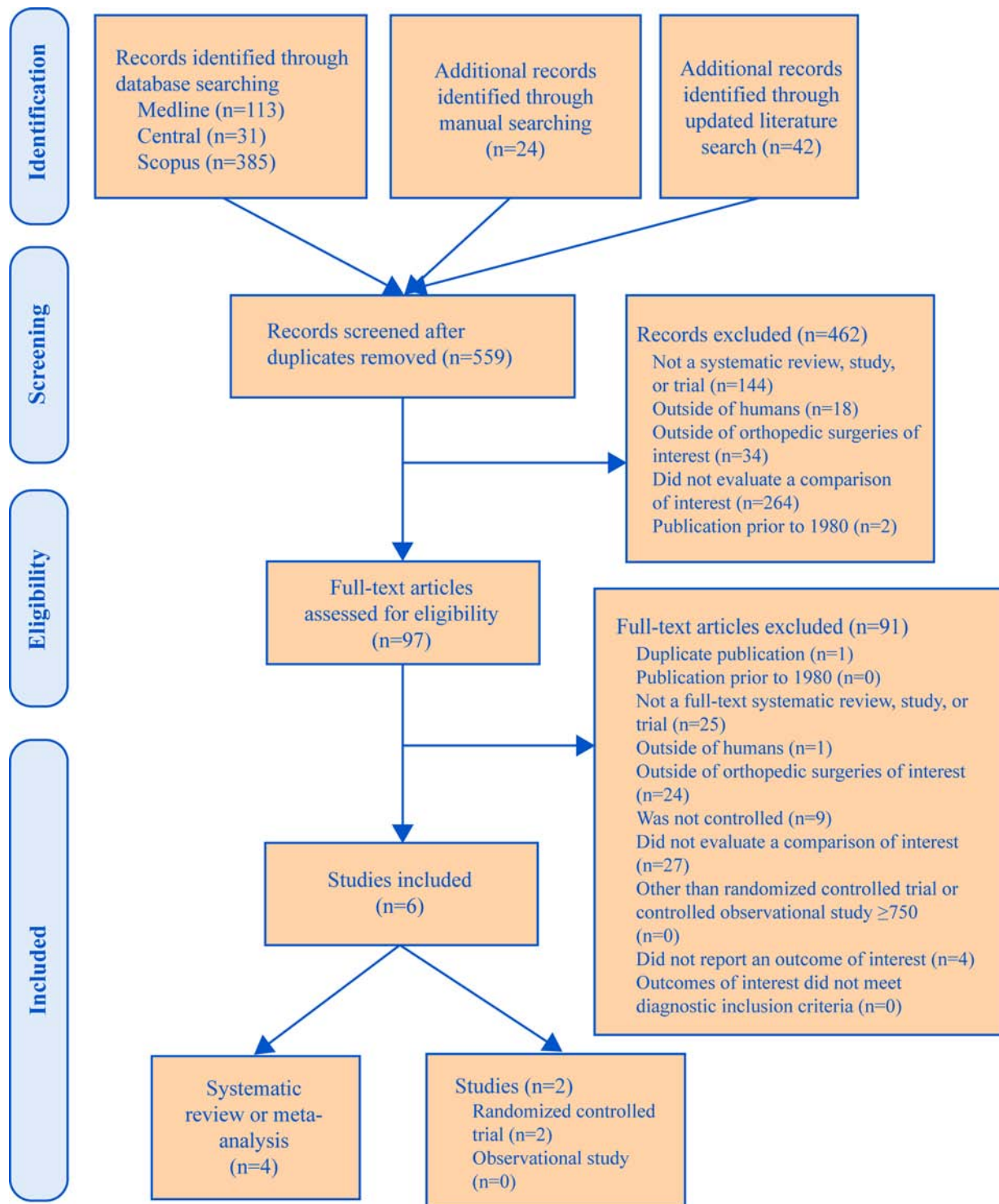


Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery*

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 1. Incidence of health outcomes in total hip replacement					
PE	5 RCT	Yes	Pooled incidence of 6% (0.3% to 18%)	L	L
DVT	8 RCT	Yes	Pooled incidence of 39% (25% to 53%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 24%		
Proximal DVT	4 RCT	Yes	Pooled incidence of 32% (14% to 54%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 14%		
Distal DVT	2 RCT	Yes	Pooled incidence of 30% (4% to 68%)	L	L
	1 RCT	No	One trial not suitable for pooling had in incidence of 17.3%		
Major bleeding	6 RCT	Yes	Pooled incidence of 1% (0.2% to 2%)	M	L
Minor bleeding	6 RCT	Yes	Pooled incidence of 5% (1% to 13%)	L	M
KQ 1. Incidence of health outcomes in total knee replacement					
PE	2 RCT	Yes	Pooled incidence of 1% (0.07% to 4%)	L	L
	1 OBS	No	The observational study had an incidence of 0.3%		
DVT	2 RCT	Yes	Pooled incidence of 46% (5% to 91%)	L	L
	1 RCT, 1 OBS	No	One trial not suitable for pooling had an incidence of 68.8% and the observational study had an incidence of 0%		
Proximal DVT	2 RCT	Yes	Pooled incidence of 17% (1% to 66%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 18.8%		
Distal DVT	2 RCT	Yes	Pooled incidence of 22% (12% to 35%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 40.6%		
Major bleeding	2 RCT	Yes	Pooled incidence of 3% (0.2% to 8%)	L	L
Minor bleeding	2 RCT	Yes	Pooled incidence of 5% (3% to 8%)	M	L
KQ 2. Impact of surgical characteristics on outcomes – general vs. regional anesthesia					
DVT	4 RCT, 2 OBS	No	The majority of trials showed that regional anesthesia was associated with a decrease in the risk of DVT while observational data were conflicting	L	L
Symptomatic DVT	2 RCT	No	No significant difference	L	L
Proximal DVT	5 RCT	No	No significant difference	L	L
KQ 2. Impact of surgical characteristics on outcomes - cemented vs. noncemented arthroplasty					
DVT	2 RCT, 3 OBS	No	No significant difference	L	L
pDVT	2 RCT	No	No significant difference	L	L
KQ 2. Impact of patient characteristics on outcomes – congestive heart failure					
Symptomatic objectively confirmed VTE	2 OBS	No	Significantly increases odds	M	M
KQ 2. Impact of patient characteristics on outcomes – age					
Symptomatic objectively confirmed VTE	2 OBS	No	No significant impact	L	M
DVT	3 OBS	No	Significantly increased risk	L	L

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery* (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Symptomatic objectively confirmed VTE					
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.70 (0.48 to 1.02)	L	M
LMWH vs. VKA	2 RCTs	Yes	No significant difference, OR 1.00 (0.69 to 1.46)	L	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.38 (0.19 to 0.77), NNT 8 to 54	M	L
KQ 4–8. Major VTE					
Pharmacologic vs. no prophylaxis	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.21 (0.05 to 0.95), NNT 19 to 22	L	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.26 (0.98 to 1.62)	M	L
KQ 4–8. PE					
Pharmacologic vs. no prophylaxis	12 RCTs	Yes	No significant difference, OR 0.38 (0.13 to 1.07)	L	L
LMWH vs. UFH	10 RCTs	Yes	Significantly decreased odds, OR 0.48 (0.24 to 0.95), NNT 8	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.18 (0.41 to 3.39)	M	L
LMWH vs. VKA	5 RCTs	Yes	No significant difference, OR 1.11 (0.57 to 2.19)	M	M
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.23 (0.56 to 18.98)	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged vs. standard duration prophylaxis	6 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.04 to 0.47), NNT 24 to 232	H	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80)		
KQ 4–8. Fatal PE					
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.90 (0.38 to 2.13)	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 1.43 (0.08 to 24.82)	L	L
KQ 4–8. Nonfatal PE					
Pharmacologic vs. no prophylaxis	6 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 0.21 (0.04 to 1.30). Observational data were supportive	L	L
LMWH vs. UFH	10 RCTs	Yes	No significant difference, OR 0.50 (0.25 to 1.00)	L	L
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.68 (0.34 to 1.37)	M	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 0.93 (0.23 to 3.66)	L	L
LMWH vs. VKA	3 RCTs	Yes	No significant difference, OR 1.00 (0.20 to 4.95)	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.27 (0.56 to 18.98)	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged vs. standard duration prophylaxis	5 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.03 to 0.54), NNT 58	M	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)		

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery* (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Mortality					
Pharmacologic vs. no prophylaxis	10 RCTs 3 OBS	Yes (RCT)	No significant difference, OR 1.23 (0.54 to 2.78). One observational study supported this finding but another study suggested decrease in number of deaths with prophylaxis	M	L
LMWH vs. UFH	8 RCTs	Yes	No significant difference, OR 0.39 (0.10 to 1.49)	M	L
LMWH vs. FXaI	5 RCTs 2 OBS	Yes (RCT)	No significant difference, OR 1.08 (0.72 to 1.60). One observational study suggested significantly higher percent of deaths in patients who received LMWH vs. factor Xa inhibitors while the other study suggested no significant difference	M	L
LMWH vs. DTI	4 RCTs	Yes	No significant difference, RR 0.45 (0.15 to 1.36)	M	L
LMWH vs. VKA	6 RCTs	Yes	No significant difference, OR 0.79 (0.42 to 1.50)	M	M
LMWH vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.31 (0.05 to 1.80)	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 7.13 (0.74 to 68.80)	L	L
KQ 4–8. DVT					
Pharmacologic vs. no prophylaxis	17 RCTs	Yes	Significantly decreased risk, RR: 0.56 (0.47 to 0.68), NNT 3 to 33	M	L
Antiplatelet vs. mechanical	2 RCTs	Yes	Significantly increased risk, RR 1.63 (1.11 to 2.39), NNH 4 to 27	M	L
LMWH vs. UFH	13 RCTs	Yes	Significantly decreased risk, RR 0.80 (0.65 to 0.99), NNT 12 to 100	M	L
	1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17)		
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, RR 1.99 (1.57 to 2.51), NNH 13 to 26	M	L
LMWH vs. VKA	5 RCTs	Yes	Significantly decreased risk, RR 0.66 (0.55 to 0.79), NNT 6 to 13	L	M
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 0.90 (0.71 to 1.14)	M	L
UFH vs. DTI	2 RCTs	Yes	Significantly increased risk, RR 2.31 (1.34 to 4.00), NNH 5 to 11	M	L
VKA vs. mechanical	3 RCTs	Yes	No significant difference, RR 1.45 (0.75 to 2.82)	L	L
Enoxaparin vs. other LMWH	2 RCTs	Yes	No significant difference, RR 1.05 (0.64 to 1.71)	L	L
IPC vs. GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.06 (0.01 to 0.41), NNT 3 to 7	L	L
Pharmacologic + mechanical vs. pharmacologic	3 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.32 to 0.72), NNT 3 to 67	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.09 (0.01 to 0.85), NNT 5		
Prolonged vs. standard duration prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.37 (0.21 to 0.64), NNT 5 to 32	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)		

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery* (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Asymptomatic DVT					
Pharmacologic vs. no prophylaxis	3 RCTs	Yes	Significantly decreased risk, RR 0.52 (0.40 to 0.69), NNT 4 to 6	M	L
LMWH vs. UFH	2 RCTs	Yes	No significant difference, RR 0.70 (0.43 to 1.16)	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 0.97 (0.85 to 1.10)	M	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.31 to 0.75), NNT 8 to 65	H	L
KQ 4–8. Symptomatic DVT					
Pharmacologic vs. no prophylaxis	4 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 1.07 (0.25 to 4.52). Observational study data were supportive	M	L
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.62 (0.22 to 1.75)	L	L
LMWH vs. FXaI	6 RCTs	Yes	No significant difference, OR 0.48 (0.21 to 1.21)	M	M
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 0.98 (0.34 to 2.87)	M	L
LMWH vs. VKA	3 RCTs	Yes	No significant difference, OR 0.87 (0.61 to 1.24)	M	L
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased odds, OR 0.36 (0.16 to 0.81), NNT 27 to 79	H	M
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)		
KQ 4–8. Proximal DVT					
Pharmacologic vs. no prophylaxis	12 RCTs	Yes	Significantly decreased risk, RR 0.53 (0.39 to 0.74), NNT 4 to 213	H	L
LMWH vs. UFH	9 RCTs	Yes	Significantly decreased risk, RR 0.60 (0.38 to 0.93), NNT 14 to 50	H	L
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, OR 2.19 (1.52 to 3.16), NNH 44 to 122	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 0.91 (0.40 to 2.11)	L	M
LMWH vs. VKA	6 RCTs	Yes	No significant difference, RR 0.63 (0.39 to 1.00)	L	M
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 0.65 (0.34 to 1.26)	M	L
UFH vs. DTI	2 RCTs	Yes	Significantly increased odds, OR 4.74 (2.99 to 7.49), NNH 11	M	L
VKA vs. mechanical	3 RCTs	Yes	Significantly decreased risk, RR 0.34 (0.16 to 0.73), NNT 11 to 31	M	L
Enoxaparin vs. other LMWH	2 RCTs	Yes	No significant difference, RR 1.06 (0.62 to 1.81)	L	L
IPC vs. GCS	2 RCTs	No	No significant difference, one trial showed RR 0.36 (0.13 to 1.00) while the second trial, which compared enoxaparin plus IPC versus enoxaparin plus GCS, showed OR 0.12 (0.01 to 1.99)	L	M
Pharmacologic + mechanical vs. pharmacologic	3 RCTs	Yes	No significant difference, RR 0.33 (0.09 to 1.22)	L	M
	2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in one trial and RR 0.09 (0.01 to 0.85) in the other trial		
Pharmacologic + mechanical vs. mechanical	2 RCTs	Yes	No significant difference, RR 0.78 (0.35 to 1.74)	L	L
Prolonged vs. standard duration prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.29 (0.16 to 0.52), NNT 9 to 71	H	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)		
KQ 4–8. Distal DVT					
Pharmacologic vs. no prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.59 (0.42 to 0.82), NNT 8 to 35	H	L

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery* (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH vs. UFH	8 RCTs	Yes	No significant difference, RR 0.95 (0.74 to 1.23)	H	L
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, RR 2.02 (1.65 to 2.48), NNH 11 to 33	H	L
LMWH vs. VKA	2 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.43 to 0.73), NNT 6 to 10	M	L
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 1.00 (0.77 to 1.29)	M	L
IPC vs. GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.07 (0.01 to 0.54), NNT 3 to 11	L	M
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons that were pooled to show RR 0.45 (0.16 to 1.26)	M	L
	1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29)		
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	No significant difference, RR 0.39 (0.15 to 1.04)	L	M
KQ 4–8. Major bleeding					
Pharmacologic vs. no prophylaxis	8 RCTs 1 OBS	Yes (RCT)	No significant difference, RR 0.74 (0.36 to 1.51) Observational data were supportive	M	L
LMWH vs. UFH	7 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.37 to 0.88), NNT 41	H	L
LMWH vs. FXaI	5 RCTs 2 OBS	Yes (RCT)	Significantly decreased odds, OR 0.65 (0.48 to 0.89), NNT 74 to 145; observational data suggested no significant difference	M	L
LMWH vs. DTI	4 RCTs	Yes	No significant difference, RR 1.12 (0.80 to 1.57)	M	L
LMWH vs. VKA	7 RCTs	Yes	Significantly increased odds, OR 1.92 (1.27 to 2.91), NNH 57 to 220	H	M
	1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed an RR 1.51 (0.92 to 2.48) for major bleeding days 0–1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2–8		
Enoxaparin vs. other LMWH	2 RCT	Yes	No significant difference, RR 1.98 (0.53 to 7.37)	M	L
Prolonged vs. standard duration prophylaxis	5 RCTs	Yes	No significant difference, OR 2.18 (0.73 to 6.51)	L	L
KQ 4–8. Major bleeding leading to reoperation					
LMWH vs. FXaI	4 RCTs	Yes	No significant difference, OR 0.67 (0.28 to 1.61)	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.27 (0.43 to 3.75)	M	L
UFH vs. DTI	2 RCTs	No	No significant difference, one trial had no events and the other trial showed OR 0.51 (0.10 to 2.55)	L	L

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery* (continued)

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Minor bleeding					
Pharmacologic prophylaxis vs. no prophylaxis	6 RCTs	Yes	Significantly increased risk, RR 1.67 (1.18 to 2.38), NNT 30 to 75	H	M
LMWH vs. UFH	5 RCTs	Yes	No significant difference, RR 0.90 (0.63 to 1.28)	M	L
LMWH vs. FXaI	2 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.35 to 0.94), NNT 31 to 60	L	
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR: 1.07 (0.89 to 1.29)	M	L
LMWH vs. VKA	7 RCTs	Yes	Significantly increased risk, RR 1.23 (1.06 to 1.43), NNH 18 to 218	M	M
	1 RCT (2 comp)	Yes	One trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0–1 and a RR 0.87 (0.37 to 2.06) on days 2–8		
VKA vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.80 (0.26 to 2.41)	L	L
Prolonged vs. standard duration prophylaxis	3 RCTs	Yes	Significantly increased odds, OR 2.44 (1.41 to 4.20), NNH 11 to 118	H	M
KQ 4–8. Surgical site bleeding					
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.92 (0.46 to 1.82)	L	L
LMWH vs. VKA	2 RCT	Yes	Significantly increased odds OR 2.63 (1.31 to 5.28), NNH 23 to 64	L	L
Enoxaparin vs. other LMWH	2 RCT	Yes	No significant difference, RR 1.35 (0.30 to 5.97)	L	L
KQ 4–8. Bleeding leading to transfusion					
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 1.00 (0.59 to 1.69)	H	L
KQ 4–8 HIT					
LMWH vs. UFH	3 RCTs	Yes	Significantly decreased odds, OR 0.12 (0.03 to 0.43), NNT 34 to 202	M	L
KQ 4–8. Readmission					
LMWH vs. UFH	2 RCT	Yes	No significant difference, RR 0.82 (0.20 to 3.38)	L	L
LMWH vs. mechanical	2 RCT	Yes	No significant difference, OR 0.83 (0.22 to 3.11)	L	L
Prolonged vs. standard duration prophylaxis	1 RCT (2 comp)	Yes	No significant difference, RR 0.29 (0.06 to 1.34)	L	L

AOE = applicability of evidence; DTI = direct thrombin inhibitor; DVT = deep vein thrombosis; FXaI = factor Xa inhibitor; H = high; IPC = intermittent pneumatic compression; KQ = Key Question; L = low; LMWH = low molecular weight heparin; M = moderate; NNH = number needed to harm; NNT = number needed to treat; OBS = observational; OR = Peto's Odds Ratio; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; UFH = unfractionated heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism

*Denotes that all base case analyses with at least one randomized controlled trial or one controlled observational study and a strength of evidence of low, moderate, or high evaluating the given outcome are represented in this table.

Table 5. Summary of previous meta-analyses evaluating the pooled incidence of outcomes of interest in patients who had major orthopedic surgery

Author, Year	N studies (N Participants)	Population	Outcome and Pooled Incidence/Risk in Placebo or Control Arms (Confidence Interval)
Brookenthal, 2001 ¹⁵³	14 (3482)	TKA	Symptomatic PE: AR 0% (0 to 10.9%) Fatal PE: AR 0% (0% to 4.2%)* DVT: AR 60.2% (55.7% to 64.5%)
Freedman, 2000 ¹⁵⁹	52 (10,929)	THA	Symptomatic PE: AR 1.51% (0.81% to 2.57%) Fatal PE: AR 0% (0% to 43%) DVT: AR 48.5% (43.4% to 53.7%) pDVT: AR 25.8% (21.4% to 30.7%) dDVT: AR 22.4% (18.8% to 26.6%) Major Bleeding: AR 0.56% (0.15% to 1.43%) Minor Bleeding: AR 3.0% (1.1% to 8.2%)
Murray, 1996 ¹⁷¹	181 papers (930,000)	THA	Fatal PE: 12% (3% to 30%)*
Imperiale, 1994 ¹⁶⁴	56 (NR)	THA	DVT: 47% (40% to 53%)† pDVT: 23% (17% to 29%)† PE: 2.4% (1.3% to 3.5%)†
Mohr, 1993 ¹⁶⁹	21 (3052)	THA	DVT: WMR 50% (NR) pDVT: WMR 24% (NR)

AR = absolute risk; CI = confidence interval; DVT = deep vein thrombosis; HFS = hip fracture surgery; NR = not reported; dDVT = distal deep vein thrombosis; N = number; pDVT = proximal DVT; PE = pulmonary embolism; sDVT = symptomatic DVT; THA = total hip arthroplasty; TKA = total knee arthroplasty; WMR = weighted mean risk

*Rates with 95% confidence interval using Poisson distribution.

†Unadjusted pooled risk.

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
Friedman, 2010 ¹⁸⁵	3 (8,210)	Population: THA and TKA Intervention 1: Dabigatran 220mg po QD Intervention 2: Dabigatran 150mg po QD Intervention 3: Enoxaparin 40mg SQ QD or 30mg SQ BID	---	---	Dabigatran 220mg versus enoxaparin Major bleeding: RD -0.2% (-0.8 to 0.5) Dabigatran 150mg versus enoxaparin Major bleeding: RD -0.4% (-1.0 to 0.2)
Tasker, 2010 ¹⁷⁹	5 (1,847)	Population: THR Intervention: LMWH Comparator: Placebo	Nonfatal PE: OR 0.14 (0.03 to 0.74) Mortality: OR 0.77 (0.15 to 3.99)	---	Major bleeding: OR 0.74 (0.23 to 2.4)
Hu, 2009 ¹⁶²	21 (NR)	Population: THR and TKR Intervention: RA Comparator: GA	PE: OR 0.46 (0.21 to 1.02) Mortality: OR 0.94 (0.14 to 6.52)	DVT: OR 0.45 (0.24 to 0.84)	----
Wolowacz, 2009* ¹⁸²	3 (8,210)	Population: THA and TKA Intervention: Dabigatran 220mg po QD Comparator: Enoxaparin 40mg SQ QD or 30mg SQ BID	VTE: RR 0.94 (0.61 to 1.44)	---	Major bleeding: RR 0.94 (0.51 to 1.75)

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8 (continued)

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
Mismetti, 2004 ¹⁶⁸	29 (NR)	Population: THR, TKR, and HFS Intervention 1: VKA Intervention 2: Antiplatelet agent Intervention 4: IPC Intervention 5: UFH Intervention 6: LMWH Intervention 7: Placebo/control	VKA versus placebo/control PE: RR 0.23 (0.09 to 0.59) Death: RR 0.78 (0.56 to 1.09) VKA versus IPC Death: RR 1.58 (0.21 to 11.7) VKA versus UFH PE: RR 0.09 (0.004 to 2.40) VKA versus LMWH PE: RR 1.10 (0.59 to 2.05) Death: RR 1.30 (0.72 to 2.36)	VKA versus placebo/control DVT: RR 0.56 (0.37 to 0.84) VKA versus antiplatelet DVT: RR 0.84 (0.55 to 1.28) pDVT: RR 1.15 (0.67 to 1.98) VKA versus IPC aDVT: RR 1.21 (0.88 to 1.66) pDVT: RR 0.46 (0.25 to 0.82) VKA versus UFH aDVT: RR 1.25 (0.87 to 1.81) VKA versus LMWH DVT: RR 1.51 (1.27 to 1.79) pDVT: RR 1.51 (1.04 to 2.17)	VKA versus placebo/control Major Hemorrhage: RR 1.53 (0.68 to 3.45) VKA versus antiplatelet Major Hemorrhage: RR 0.98 (0.04 to 25) VKA versus IPC Major Hemorrhage: RR 1.77 (0.14 to 23) VKA versus LMWH Major Hemorrhage: RR 0.78 (0.49 to 1.26)
Muntz, 2004 ¹⁷⁰	21 (20,523)	Population: THR, TKR, or HFS Intervention 1: LMWH Intervention 2: VKAs (warfarin and other coumarin derivatives) Intervention 3: UFH	---	---	VKAs versus LMWH Major Bleeding: RR 0.59 (0.44 to 0.80) UFH versus LMWH Major Bleeding: RR 1.52 (1.04 to 2.23)
Turpie, 2004 ¹⁸⁹ and 2002 ¹⁸⁰	4 (7,344)	Population: TKR, THR and HFS Intervention: Fondaparinux 2.5mg SQ QD Comparator: Enoxaparin (approved regimens)	VTE: Odds reduction: 49.6% (27.3 to 65.5) VTE: Odds reduction: 48.0% (27.3 to 63.2)	pDVT: Odds reduction: 57.4% (35.6 to 72.3)	

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8 (continued)

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
O'Donnell, 2003 ¹⁷⁴	2 (907)† 5 (1,917) 7 (2,425)	Population: THA Intervention 1: Extended LMWH therapy after completion of an initial 7 to 12 days of prophylaxis after surgery Intervention 2: placebo/control	sVTE (3m): OR 0.39 (0.14 to 1.11) sPE (3m): ARR 0.36% (-.3% to 1.36%) Fatal PE (3m): ARR 0.09% (-0.08% to 0.27%)	---	---
Zufferey, 2003 ¹⁸⁴	13 (1,925)	Population: THR, TKR, and HFS Intervention: LMWH (3000 anti-Xa IU to 6000 anti-Xa IU daily) Comparator: Placebo	---	aDVT: RR 0.51 (0.45 to 0.59)	Major hemorrhage: RR 0.80 (0.36 to 1.79)
Handoll, 2002† ¹⁶⁰	31 (2,958)	Population: HFS Intervention 1: LMWH Intervention 2: UFH Intervention 3: LMWH or UFH Intervention 4: Mechanical methods (IPC and VFP) Intervention 5: Placebo or control	LMWH or UFH versus placebo/control PE: RR 1.00 (0.49 to 2.02) Nonfatal PE: RR 4.94 (1.10 to 22.07) Fatal PE: RR 0.47 (0.19 to 1.14) Death: RR 1.16 (0.77 to 1.74) Mechanical versus control PE: RR 0.40 (0.17 to 0.96) Fatal PE: RR 0.27 (0.07 to 1.08) Death: RR 0.50 (0.22 to 1.14) LMWH versus UFH PE: RR 3.29 (0.82 to 13.32) Nonfatal PE: RR 12.42 (0.72 to 213.88) Death: RR 0.85 (0.31 to 2.36)	LMWH or UFH versus placebo/control DVT: RR 0.60 (0.50 to 0.71) pDVT: RR 0.45 (0.28 to 0.73) dDVT: RR 0.65 (0.47 to 0.89) UFH versus placebo/control DVT: OR 0.41 (0.30 to 0.56) Mechanical versus control DVT: RR 0.31 (0.19 to 0.51) pDVT: RR 0.22 (0.10 to 0.53) dDVT: RR 0.45 (0.23 to 0.85) LMWH versus UFH DVT: RR 0.67 (0.48 to 0.94) pDVT: RR 0.84 (0.47 to 1.48) dDVT: RR 0.68 (0.23 to 2.00)	---

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8 (continued)

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
Cohen, 2001 ¹⁸⁶	6 (NR)	Population: Hip or knee arthroplasty Intervention: LMWH or warfarin followed by additional LMWH prophylaxis (total 4-5 weeks) Comparator: LMWH or warfarin (7-15 d) followed by placebo	VTE: OR 0.50 (0.30 to 0.83)	---	---
Eikelboom, 2001 ¹⁵⁶	9 (3,999)	Population: THR and TKR Intervention: Extended-duration prophylaxis with LMWH or UFH (30d-42d) Comparator: Standard-duration prophylaxis with LMWH or UFH	PE: OR 0.43 (0.17 to 1.06) Death: OR 0.68 (0.25 to 1.88)	sDVT: OR 0.41 (0.24 to 0.68) aDVT: OR 0.48 (0.36 to 0.63)	Major bleeding: OR 0.62 (0.22 to 1.75) Minor bleeding: OR 1.56 (1.08 to 2.26)
Hull, 2001 ¹⁶³	6 (1,953)	Population: Elective hip arthroplasty Intervention: LMWH in and out of hospital Comparator: LMWH in hospital then placebo	---	DVT: RR 0.41 (0.32 to 0.54) pDVT: RR 0.31 (0.20 to 0.47) sDVT: RR 0.36 (0.20 to 0.67)	---

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8 (continued)

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
Westrich, 2000 ¹⁸¹	23 (6,001)	Population: TKA Intervention 1: ASA 325mg to 650mg po QD Intervention 2: Warfarin (PT 1.3 to 1.5 of normal) Intervention 3: LMWH Intervention 4: IPC	ASA versus warfarin aPE: OR 1.2 (NR) sPE: OR 2.1 (0.9 to 4.8) ASA versus LMWH sPE: OR 2.7 (0.5 to 14) ASA versus IPC aPE: OR 2.5 (1.7 to 3.8) sPE: OR 6.5 (0.4 to 106) Warfarin versus LMWH sPE: OR 1.8 (0.2 to 14) Warfarin versus IPC aPE: OR 1.7 (1.1 to 2.6) sPE: OR 3.0 (0.2 to 53) LMWH versus IPC sPE: OR 2.4 (0.1 to 59)	ASA versus warfarin DVT: OR 1.7 (1.5 to 1.9) ASA versus LMWH DVT: OR 3.47 (3.04 to 3.96) ASA versus IPC DVT: OR 3.2 (2.7 to 3.8) Warfarin versus LMWH DVT: OR 2.05 (1.76 to 2.39) Warfarin versus IPC DVT: OR 1.9 (1.6 to 2.3) LMWH versus IPC DVT: OR 1.09 (0.9 to 1.33)	---
Howard, 1998 ¹⁶¹	10 (3,079)	Population: TKA Intervention 1: LMWH Intervention 2: Warfarin Intervention 3: UFH Intervention 4: Placebo	---	LMWH versus placebo DVT: RR 0.42 (0.26 to 0.67) pDVT: RR 0.11 (0.03 to 0.40) LMWH versus warfarin DVT: RR 0.71 (0.64 to 0.80) pDVT: RR 0.67 (0.43 to 1.04) LMWH versus UFH DVT: RR 0.76 (0.60 to 0.95) pDVT: RR 0.32 (0.13 to 0.80)	---
Anderson, 1993 ¹⁵²	6 (1,420)	Population: THA Intervention: LMWH Comparator: UFH	sPE: OR 0.22 (0.05 to 0.88)	DVT: OR 0.72 (0.53 to 0.95) pDVT: OR 0.40 (0.28 to 0.59) dDVT: OR 1.21 (0.86 to 1.74)	Major bleeding: OR 0.64 (0.34 to 1.23) Minor bleeding: OR 0.92 (0.61 to 1.33)

Table 6. Summary of results from previous meta-analyses relevant to Key Questions 2 through 8 (continued)

Author, Year	N studies (N Subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse Outcomes
Leizorovicz, 1992 ¹⁸⁸	23 (3,976) [§] 5 (595) 14 (2,692)	Population: Elective or nonelective orthopedic surgery Intervention 1: LMWH SQ QD Intervention 2: UFH Intervention 3: Placebo	LMWH versus placebo PE: OR 0.64 (0.08 to 5.03) Mortality: OR 0.92 (0.18 to 4.62) LMWH versus UFH PE: OR 0.53 (0.27 to 1.03) Mortality: OR 0.88 (0.37 to 2.07)	LMWH versus placebo DVT: OR 0.32 (0.22 to 0.46) LMWH versus UFH DVT: OR 0.83 (0.68 to 1.02)	LMWH versus placebo Bleeding: OR 0.69 (0.22 to 2.11) LMWH versus UFH Bleeding: OR 1.09 (0.76 to 1.58)
Nur-mohamed, 1992 ¹⁸⁷	6 (1,294)	Population: Elective or traumatic hip surgery Intervention: LMWH Comparator: UFH	PE: RR 0.43 (0.22 to 0.82)	DVT: RR 0.68 (0.54 to 0.86)	Major bleeding: RR 0.75 (0.26 to 2.14)

aDVT = asymptomatic deep vein thrombosis; aPE = asymptomatic pulmonary embolism; ARR = absolute risk reduction; ASA = aspirin; d = days; dDVT = distal deep vein thrombosis; DVT = deep vein thrombosis; GA = general anesthesia; HFS = hip fracture surgery; IPC = intermittent pneumatic compression; IU = international units; LMWH = low molecular weight heparin; m = months; mg = milligram; NR = not reported; OR = odds ratio; PE = pulmonary embolism; pDVT = proximal deep vein thrombosis; po = by mouth; PT = prothrombin time; QD = daily; RA = regional anesthesia; sDVT = symptomatic deep vein thrombosis; sPE = symptomatic pulmonary embolism; SQ = subcutaneous; sVTE = symptomatic venous thromboembolism; THA = total hip arthroplasty; THR = total hip replacement; TKA = total knee arthroplasty; TKR = total knee replacement; UFH = unfractionated heparin; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism; WMI = weighted mean incidence; Xa = factor 10a

*Results of random effects model.

†The number of studies and subjects varied based on the outcome reported and follows this order: sVTE, sPE, fatal PE.

‡Results are presented with 99% confidence intervals.

§The number of studies and subjects varied based on the comparison and follows this order: LMWH versus placebo, LMWH versus UFH.

--- Not reported.

Key Question 1

In patients undergoing major orthopedic surgery (total hip replacement, total knee replacement or hip fracture surgery) what is the baseline postoperative risk of venous thromboembolism outcomes (symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, deep vein thrombosis, asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep vein thrombosis, distal deep vein thrombosis) and bleeding outcomes (major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, and bleeding leading to transfusion) in contemporary practice?

Key Points

- The impact of orthopedic surgery on pulmonary embolism, deep vein thrombosis, and bleeding is most extensively evaluated in clinical trials for total hip replacement followed by total knee replacement and then hip fracture surgery. To determine the impact of surgery on venous thromboembolism, pulmonary embolism, or deep vein thrombosis we only allowed trial arms where no prophylaxis was given (either control or placebo) but for bleeding outcomes we also allowed trial arms with mechanical prophylaxis since the risk of bleeding is not impacted by these methods.
- Only evaluating trials and studies conducted from 1980 to the present limits the available literature base but likely reflects more contemporary practice. Only evaluating trials and studies with rigorous definitions of pulmonary embolism and deep vein thrombosis limits the available literature base and decreases the number of events that might be reported through the use of laxer definitions.
- We still had high statistical heterogeneity between trials for most endpoints which likely reflects several study characteristics. The majority of trials did not specifically define the duration of followup and implied an immediate postoperative followup, although this could vary between studies. Additionally, the followup period may not reflect the period of highest risk for venous thromboembolic events after major orthopedic surgery. The year in which studies were conducted ranged from 1980 to 2011, with most studies published prior to 2000, and may reflect changes in patient care and clinical practice. The countries and ethnicities where the trials were conducted in and when or how rigorously the endpoints were assessed for also varied.
- Not all three surgeries had incidence data reported in clinical trials for each outcome therefore when no data were available for an outcome and surgery, the symbol “--” is used. In total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, respectively, the postoperative incidence of pulmonary embolism (6 percent, 1 percent, 3 percent), deep vein thrombosis (39 percent, 46 percent, 47 percent), proximal deep vein thrombosis (32 percent, 17 percent, --), distal deep vein thrombosis (30 percent, 22 percent, --), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (5 percent, 5 percent, --) major bleeding leading to reoperation (0 percent, 0 percent, --), and major bleeding leading to transfusion (0 percent, 0 percent, --) are reported in clinical trials. While the incidence of deep vein thrombosis events is relatively high, pulmonary embolism and bleeding events are rarer.

- The strength of the evidence is predominately low for hip and knee replacement surgery, however was insufficient for all outcomes within hip fracture surgery.
- No trials evaluated the following venous thromboembolism outcomes (symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis), and bleeding outcomes (surgical site bleeding, bleeding leading to infection).

Detailed Analysis

Study Design and Characteristics

Nineteen randomized controlled trials (N=1325) and three controlled observational studies (N=1036) evaluated the overall baseline risk of venous thromboembolism outcomes and bleeding outcomes in contemporary practice.^{21,34-36,38,40,41,43,44,47,49-51,53,76,90,132,133,135,144,146,150} All nineteen randomized controlled trials were published as full text manuscripts. Thirteen randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing total hip arthroplasty.^{21,34,35,38,41,44,47,49,50,76,90,133,135} Five randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing total knee arthroplasty.^{36,38,43,51,53} Two randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing hip fracture surgery. The earliest trial was published in 1980 while the most recent published in 2011.^{43,135} The duration of followup ranged from the postoperative period to 2.4 years. Three trials received funding from industry,^{38,53,133} five trials received funding from government and foundation,^{34,49,50,76,90} one trial received funding from industry and government,¹³² one trial received funding from government,³⁵ and in nine trials the funding source was not reported.^{21,36,40,41,43,44,47,51,135}

The mean age of enrolled patients ranged from 54.9 years to 80 years. Females represented between 18.0 to 91.81 percent of the enrolled populations. The mean weight ranged from 56 to 71.4 kilograms. Few patients enrolled had a history of venous thromboembolism, with the majority of trials reporting 0 to 10.0 percent. Presence of varicosity was ranged from no varicosity to 33.3 percent. The percent of patients with a history of malignancy ranged from 0 to 7.14 percent. None of the trials reported the percent of patients who had previously undergone orthopedic surgery.

Eighty to 100 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 0 to 100 percent. Mean duration of surgery ranged from 60 to 147 minutes and the mean duration of anesthesia was only reported by one trial with 205 minutes for the control group. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 0 to 100 percent of patients and regional anesthesia use ranging from 0 to 100 percent of patients. The mean length of hospital stay was infrequently reported, and when it was ranged from 7.9 to 16 days.

Three controlled observational studies (N=1036) evaluated the overall baseline risk of venous thromboembolism outcomes and bleeding outcomes in contemporary practice.^{144,146,150} All of these unfunded observational studies were published as full text manuscripts. First study was conducted in people undergoing total hip or total knee arthroplasty and those without chemical prophylaxis (N=136) all had contraindications to receive aspirin therapy which may not be representative of the natural course of embolization or bleeding.¹⁴⁴ It was not explicitly stated whether or not mechanical approaches could have been used in these patients. The second study

was conducted in people undergoing total knee arthroplasty and those with no pharmacological or mechanical prophylaxis (N=785). Since they were derived mostly from orthopedic practices where a lack of prophylaxis is routine, it is not subject to the same confounds as the first observational study.¹⁴⁶ The third study was conducted among patients who underwent total hip arthroplasty, total knee arthroplasty, or hip fracture surgery (N=115). Episodes of major bleeding were identified using ICD-90-CM diagnosis codes.¹⁵⁰

Outcome Evaluation

A summary of the baseline risk of venous thromboembolism and bleeding outcomes during the postoperative period from included trials is presented in Table 7 to Table 9. The majority of trials did not specifically define the duration of followup and implied an immediate postoperative followup therefore the period for which these incidences reflect is likely the immediate postoperative period rather than longer term. Five trials evaluated the occurrence of pulmonary embolism among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis (patients were randomly allocated to control or placebo).^{21,34,35,49,50} In these trials, the pooled incidence of pulmonary embolism was 6 percent [0.06 (95 percent CI=0.003 to 0.18)]. A high level of statistical heterogeneity was detected ($I^2=88.8$ percent), but publication bias was not found (Egger's $P=0.106$). Only one trial evaluated the occurrence of fatal and nonfatal pulmonary embolism.⁴⁹ In this trial, 0 out of 50 patients (0 percent) developed fatal pulmonary embolism and 1 out of 50 patients (2 percent) developed nonfatal pulmonary embolism.

Two trials evaluated the occurrence of pulmonary embolism among patients undergoing total knee arthroplasty who received no pharmacologic or mechanical prophylaxis (patients were randomly allocated to control or placebo).^{36,51} In these trials, the pooled incidence of pulmonary embolism was 1 percent [0.01 (95 percent CI=0.0007 to 0.04)]. Out of these trials, one trial also evaluated the occurrence of fatal and nonfatal pulmonary embolism.⁵¹ In this trial no patients developed fatal or nonfatal pulmonary embolism.

In hip fracture surgery, 2 of 63 patients (3 percent) who received no pharmacologic or mechanical prophylaxis developed pulmonary embolism in the only available trial.¹³² Both of the pulmonary embolism events were nonfatal.

Eight trials evaluated the occurrence of deep vein thrombosis among patients who received no pharmacologic or mechanical prophylaxis undergoing total hip arthroplasty.^{21,34,35,41,47,49,50,133} In these trials, the pooled incidence of deep vein thrombosis was 39 percent [0.39 (95 percent CI=0.25 to 0.53)]. A high level of statistical heterogeneity was detected ($I^2=85.6$ percent), but publication bias was not found (Egger's $P=0.118$). Four trials evaluated the occurrence of proximal deep vein thrombosis among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis.^{21,34,49,133} In these trials, the pooled incidence of proximal deep vein thrombosis was 32 percent [0.32 (95 percent CI=0.14 to 0.54)]. A high level of statistical heterogeneity and publication bias were detected ($I^2=87.2$ percent, Egger's $P=0.030$), although the directionality of the publication bias was unclear. Two trials evaluated the occurrence of distal deep vein thrombosis among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis.^{21,34} In these trials, the pooled incidence of distal deep vein thrombosis was 30 percent [0.30 (95 percent CI=0.04 to 0.68)]. In the trial by Kim and colleagues in 2003, the authors also determined the risk of deep vein thrombosis among patients who could have had more than one hip operated on. These data were not suitable for pooling but deep vein thrombosis, proximal deep vein thrombosis, and distal

deep vein thrombosis occurred in 72 of 300 hips (24 percent), 42 of 300 hips (14 percent), and 52 of 300 hips (17.3 percent) operated on.²¹

Three trials evaluated the occurrence of deep vein thrombosis among patients undergoing total knee arthroplasty who received no pharmacologic or mechanical prophylaxis.^{36,43,51} However the trial by Wilson and colleagues was not suitable for pooling because the incidence was reported out of legs rather than patients. In the remaining two trials, the pooled incidence of deep vein thrombosis was 46 percent [0.46 (95 percent CI=0.05 to 0.91)]. The same two trials evaluated the occurrence of proximal deep vein thrombosis and distal deep vein thrombosis among patients undergoing total knee arthroplasty who received no prophylaxis.^{36,43} In these trials, the pooled incidence of proximal deep vein thrombosis was 17 percent [0.17 (95 percent CI=0.01 to 0.66)] and the pooled incidence of distal deep vein thrombosis was 22 percent [0.22 (95 percent CI=0.12 to 0.35)].^{36,43} In a trial by Wilson and colleagues, patients who had one or more total knee replacements had a deep vein thrombosis, proximal deep vein thrombosis and distal deep vein thrombosis in 22 of 32 legs (68.8 percent), 6 of 32 legs (18.8 percent), and 13 of 32 legs (40.6 percent), respectively.⁵¹

One trial evaluated the occurrence of deep vein thrombosis among patients undergoing hip fracture surgery who received no pharmacologic or mechanical prophylaxis.⁴⁰ The pooled incidence of deep vein thrombosis could not be calculated because only one study was available. In this trial, 18 out of 38 patients (47 percent) undergoing hip fracture surgery developed deep vein thrombosis. No trials evaluated the occurrence of proximal or distal deep vein thrombosis among patients undergoing hip fracture surgery who received no pharmacologic or mechanical prophylaxis.

Six trials evaluated the occurrence of major bleeding among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis.^{38,41,44,49,90,135} In these trials, the pooled incidence of major bleeding was 1 percent [0.01 (95 percent CI=0.002 to 0.02)]. A low level of statistical heterogeneity was detected as was the presence of publication bias detected ($I^2=12.3$ percent, Egger's $P=0.040$). The direction of publication bias suggests that there may be underestimation of the occurrence of major bleeding. Six trials evaluated the occurrence of minor bleeding among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis.^{38,44,49,76,90,135} In these trials, the pooled incidence of minor bleeding was 5 percent [0.05 (95 percent CI=0.01 to 0.13)]. A high level of statistical heterogeneity was detected ($I^2=88.1$ percent). Publication bias was detected as well, suggesting an underestimation in the incidence of minor bleeding (Egger's $P=0.008$). In the two trials that evaluated the occurrence of major bleeding leading to reoperation among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis, no events occurred.^{44,76} In the one trial that evaluated bleeding leading to transfusion no events occurred.⁷⁶

Two trials evaluated the occurrence of major bleeding among patients undergoing total knee arthroplasty who received either no prophylaxis or only mechanical prophylaxis.^{38,53} In these two trials, the pooled incidence of major bleeding was 3 percent [0.03 (95 percent CI=0.002 to 0.08)]. Two trials evaluated the occurrence of minor bleeding among patients undergoing total knee arthroplasty who received either no prophylaxis or only mechanical prophylaxis.^{38,53} In these two trials, the pooled incidence of minor bleeding was 5 percent [0.05 (95 percent CI=0.03 to 0.08)]. In the one trial that evaluated the occurrence of major bleeding leading to reoperation among patients undergoing total knee arthroplasty who received either no prophylaxis or only

mechanical prophylaxis, no events occurred.⁵³ In the one trial that evaluated bleeding leading to transfusion no events occurred.⁵³

One trial evaluated the occurrence of major bleeding among patients undergoing hip fracture surgery who received either no prophylaxis or only mechanical prophylaxis.¹³² In this trial, 5 out of 63 patients (8 percent) undergoing hip fracture surgery developed major bleeding. No trials evaluated the occurrence of minor bleeding, major bleeding leading to reoperation or major bleeding leading to transfusion in this population.

In the first observational study, incidence of fatal pulmonary embolism, nonfatal pulmonary embolism, and deep venous thrombosis after total hip or total knee arthroplasty were 0 percent, 0 percent, and 1.5 percent, respectively.¹⁴⁴ However, these patients all had contraindications to aspirin prophylaxis and might not be representative of the overall population undergoing orthopedic surgery. It is also not clear whether or not mechanical prophylaxis was allowed. In the second observational study, there was no occurrence of deep vein thrombosis but 2 of 785 patients (0.3 percent) undergoing total knee arthroplasty developed pulmonary embolism, both episodes were nonfatal.¹⁴⁶ In the third observational study, the incidence of major bleeding was 0.9 percent among patients undergoing total hip arthroplasty, total knee arthroplasty, or hip fracture surgery.

Strength of Evidence and Applicability of the Body of Evidence

The majority of incidences of health outcomes and adverse events in the major orthopedic surgery population presented in Key Question 1 had strength of evidence rating of low or insufficient. All outcomes evaluated for hip fracture surgery were rated with insufficient evidence. As randomization was broken to pool data from placebo and control arms the risk of bias was inherently higher. Although each major orthopedic surgery was considered separately, high statistical heterogeneity was observed between trials for most endpoints which likely reflect the different time periods of followup, the countries and ethnicities where the trials were conducted in and when or how rigorously the endpoints were assessed for. In total hip replacement, there was moderate strength of evidence for the incidence of major bleeding although the strength of evidence was low for incidence of pulmonary embolism, deep vein thrombosis, proximal deep vein thrombosis, distal deep vein thrombosis, and minor bleeding. In total knee replacement surgery, the strength of evidence was moderate for the incidence of minor bleeding while low for the incidences of pulmonary embolism, deep vein thrombosis, proximal deep vein thrombosis, distal deep vein thrombosis, and major bleeding. For all outcomes evaluated in hip fracture surgery, data were insufficient while in total hip and knee replacement surgery data were insufficient for symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, fatal or nonfatal pulmonary embolism, asymptomatic or symptomatic deep vein thrombosis, major bleeding leading to reoperation, surgical site bleeding, bleeding leading to infection or leading to transfusion in either total hip or knee replacement surgery.

The overall applicability was low for all outcomes with exception of major bleeding, minor bleeding and bleeding leading to transfusion in total hip replacement surgery which had moderate applicability. Although each major orthopedic surgery was considered separately when estimating the incidence of outcomes, the majority of trials and in many cases the only trials available were conducted outside of the United States. Surgical and post surgical characteristics, training, and expertise in other countries may not reflect that within the United States. Additionally, some trials were conducted in the 1980s as opposed to the 1990s or within the

2000's, which may be subject changes in surgical techniques and patient care over time. Given the general description of the followup period in the majority of trials, the presented incidences likely reflect a more immediate postoperative period rather than a long term followup.

Table 7. The overall baseline risk of venous thromboembolism and bleeding outcomes in patients undergoing major orthopedic surgery limited to hip replacement surgery

Author, Year	PE	Fatal PE	Nonfatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major Bleeding Leading to Reoperation	Bleeding Leading to Transfusion
Yokote, 2011 ¹³⁵	---	---	---	---	---	---	0/85 (0.0%)	2/85 (2.4%)	---	---
Fuji, 2008 ³⁸	---	---	---	---	---	---	0/101 (0.0%)	2/101 (2.0%)	---	---
Kim, 2003 ²¹	0/200 (0.0%)	---	---	20/100 (20.0%)	12/100 (12.0%)	14/100 (14.0%)	---	---	---	---
Kim, 1998 ⁴¹	---	---	---	10/50 (20.0%)	---	---	0/50 (0.0%)	---	---	---
Samama, 1997 ⁴⁴	---	---	---	---	---	---	1/75 (1.3%)	21/75 (28.0%)	0/75 (0.0%)	---
Kalodiki, 1996 ¹³³	---	---	---	13/14 (92.9%)	8/14 (57.1%)	---	---	---	---	---
Francis, 1992 ⁷⁶	---	---	---	---	---	---	---	4/98 (4.1%)	0/98 (0.0%)	0/98 (0.0%)
Torholm, 1991 ⁴⁷	---	---	---	16/54 (29.6%)	---	---	---	---	---	---
Paiment, 1987 ⁹⁰	---	---	---	---	---	---	0/66 (0.0%)	3/66 (4.5%)	---	---
Alfaro, 1986 ³⁵	1/30 (3.3%)	---	---	9/30 (30.0%)	---	---	---	---	---	---
Turpie, 1986 ⁴⁹	1/50 (2.0%)	0/50 (0.0%)	1/50 (2.0%)	20/39 (51.3%)	9/39 (23.1%)	---	2/50 (4.0%)	0/50 (0.0%)	---	---
Welin-Berger, 1982 ⁵⁰	1/20 (5.0%)	---	---	5/20 (25.0%)	---	---	---	---	---	---
Modig, 1981 ³⁴	9/30 (30.0%)	---	---	16/30 (53.3%)	14/30 (46.7%)	15/30 (50.0%)	---	---	---	---

DVT = deep vein thrombosis; PE = pulmonary embolism

--- No data.

Table 8. The overall baseline risk of venous thromboembolism and bleeding outcomes in patients undergoing major orthopedic surgery limited to knee replacement surgery

Author, Year	PE	Fatal PE	Nonfatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major Bleeding Leading to Reoperation	Bleeding Leading to Transfusion
Fuji, 2010 ⁵³	---	---	---	---	---	---	1/124 (0.8%)	6/124 (4.8%)	0/124 (0.0%)	0/124 (0.0%)
Chin, 2009 ³⁶	1/110 (0.9%)	---	---	24/110 (21.8%)	3/110 (2.7%)	21/110 (19.1%)	---	---	---	---
Fuji, 2008 ³⁸	---	---	---	---	---	---	4/89 (4.5%)	4/89 (4.5%)	---	---
Wilson, 1992 ⁵¹	0/32 (0.0%)	0/32 (0.0%)	0/32 (0.0%)	22/32 (68.8%)*	6/32 (18.8%)*	13/32 (40.6%)*	---	---	---	---
McKenna, 1980 ⁴³	---	---	---	9/12 (75.0%)	5/12 (41.7%)	4/12 (33.3%)	---	---	---	---

DVT = deep vein thrombosis; PE = pulmonary embolism

*Denotes events per total number of legs operated on rather than total number of people

--- No data.

Table 9. The overall baseline risk of venous thromboembolism and bleeding outcomes in patients undergoing major orthopedic surgery limited to hip fracture surgery

Author, Year	PE	Fatal PE	Nonfatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major Bleeding Leading to Reoperation	Bleeding Leading to Transfusion
Jorgensen, 1992 ⁴⁰	---	---	---	18/38 (47.4%)	---	---	---	---	---	---
Powers, 1989 ¹³²	2/63 (3.2%)	0/63 (0.0%)	2/63 (3.2%)	---	---	---	5/63 (7.9%)	---	---	---

DVT = deep vein thrombosis; PE = pulmonary embolism

--- No data.

Key Question 2

In patients undergoing major orthopedic surgery (total hip replacement, total knee replacement or hip fracture surgery) what patient, surgical or postsurgical characteristics predict or differentiate patient risk of venous thromboembolic and bleeding outcomes in contemporary practice?

Key Points

- Sixteen randomized controlled trials and four observational studies evaluated the impact of surgical characteristics on venous thromboembolic or bleeding outcomes.
- Data were insufficient for all surgical or postsurgical characteristics with the exception of two comparisons; general versus regional anesthesia and cemented versus noncemented arthroplasty, in which there was a low strength of evidence.
 - There was low strength of evidence that patients who had general anesthesia had a higher risk of deep vein thrombosis compared with regional anesthesia while there was no difference in the risk of proximal or distal deep vein thrombosis compared with regional anesthesia. Data were insufficient to evaluate the impact on the risk of pulmonary embolism, asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, major bleeding and minor bleeding or the comparison of spinal versus regional anesthesia and the risk of deep vein thrombosis.
 - There was also low strength of evidence that patients who had cemented arthroplasty had no difference in the risk of deep vein thrombosis or proximal deep vein thrombosis compared with noncemented arthroplasty. Data were insufficient to evaluate the impact on pulmonary embolism and on the risk of deep vein thrombosis.
 - Data were insufficient to evaluate the following relationships: bone vacuum cement versus standard procedure and the risk of deep vein thrombosis, proximal or distal deep vein thrombosis, major bleeding, and minor bleeding; tourniquet use versus no use on the risk of asymptomatic or symptomatic or distal deep vein thrombosis; early versus late tourniquet release on the risk of deep vein thrombosis; modified limb position on the risk of deep vein thrombosis, proximal deep vein thrombosis, or pulmonary embolism; tissue fibrin use versus no tissue fibrin on the risk of fatal pulmonary embolism or deep vein thrombosis; primary versus revision surgery on the odds of deep vein thrombosis, perioperative blood loss, operative time, or blood transfusions.
- Eleven observational studies evaluated the impact of patient characteristics on venous thromboembolic or bleeding outcomes all using multivariate regression analysis. Overall few patient characteristics were evaluated by more than one study for each outcome of interest.
- Overall data were insufficient for all patient characteristics with the exception of two; congestive heart failure and age.
 - There was moderate strength of evidence that congestive heart failure increased the odds of symptomatic objectively confirmed venous thromboembolism.

- There was low strength of evidence that age did not impact the odds of symptomatic objectively confirmed venous thromboembolism and increased the odds of deep vein thrombosis, in major orthopedic surgery.
- Data were insufficient to evaluate most patient characteristics including the following:
 - The odds of symptomatic objectively confirmed venous thromboembolism were increased by inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric or subtrochanteric fractures (one study), increased hemoglobin on admission (one study), personal or familial history of venous thromboembolism (one study), and varicose veins (one study) while those showing no effect on the odds included male gender (one study).
 - The odds of pulmonary embolism were increased by age and genitourinary tract infection, decreased by cardiovascular disease, and unaffected by a history of phlebitis, phlebitis in the opposite extremity, thyroid hormone replacement therapy, history of pulmonary embolism, varicosity, or peripheral vascular disease, each evaluated in one study.
 - The odds of deep vein thrombosis were uninfluenced by height, weight, Factor V Leiden mutation (each evaluated in one study), and mixed effects were seen with age (three studies), obesity (two studies), and gender (two studies). Smoking was reported in one study to have little to no effect although magnitude and direction of effect was not reported.
 - The odds of symptomatic deep vein thrombosis were consistently increased by metabolic syndrome while were consistently unaffected by age, gender, education, diabetes mellitus, hypertension, hyperlipidemia, body mass index, and presence of comorbidities.
 - The odds of proximal deep vein thrombosis were increased by congestive heart failure (one study) while were unaffected by age (two studies), prior deep vein thrombosis (one study), inactive malignancy (one study), current hormone replacement therapy (one study), chronic tobacco use (one study), and blood disorders defined as sickle-cell trait, polycythemia vera, and thrombocytopenia (one study).
 - The one study which evaluated major bleeding suggested that age, gender, risk of bleeding, specific surgical procedure (total hip, knee replacement or hip fracture surgery), and prophylaxis administered in the hospital significantly impacted the risk of major bleeding. However, the magnitude and direction of the effect was not specified.

Detailed Analysis

Study Design and Characteristics

Sixteen randomized controlled trials (N=1777), seven controlled observational studies (N=18152) and four nested observational studies (N=2469) evaluated the impact of patient, surgical, or postsurgical characteristics on the risk of venous thromboembolic or bleeding outcomes.^{18-24,26,28-34,56,68,73,117,136-141,150,197} All sixteen randomized controlled trials evaluated surgical characteristics and were published as full text manuscripts. Six trials compared general with regional anesthesia,^{20,24,30,32,34,197} one trial compared spinal with epidural anesthesia,¹⁹ three trials evaluated cemented arthroplasty techniques,^{21,22,26,68} three trials evaluated aspects of

tourniquet use during surgery,^{28,31,33} two trials evaluated limb positioning^{18,29} and one trial evaluated tissue fibrin adhesive.²³ Six trial enrolled patients who had total hip replacement surgery (n=773),^{18,21,22,26,34,197} nine trials enrolled patients who had total knee replacement surgery (n=964),^{19,20,23,24,28-31,33} and one trial enrolled patients who had hip fracture surgery (n=40).³² The earliest trial was published 1981 while the most recent in 2008. The duration of followup ranged from the postoperative time period to one year. One trial was funded by industry,²⁶ two trials were funded by government/foundation,^{22,30} two trials were funded by government/foundation and industry^{20,34} two trials were unfunded,^{23,33} seven trials did not disclose funding source,^{18,19,21,24,28,31,32,197}

The mean age of patients ranged from 54.9 to 73.9 years.^{21,32} Females represented between 37.5 to 81.0 percent of the enrolled population.^{19,24} Mean weight ranged from 68.7 to 100 kilograms.^{19,197} History of venous thromboembolism ranged from zero percent to 10 percent.^{20,26,28-30,33,34} Other baseline characteristics were scarcely reported. Eight studies evaluated exclusively patients who had primary surgery.^{18,22,24,26,29-31,197} Mean hospital length of stay was reported in four trials and ranged from 10.4 to 12.7 days.^{24,26,30,31} Mean duration of surgery ranged from 51 to 161.3 minutes.^{28,34}

Eleven controlled observational studies evaluated the impact of patient and surgical characteristics on the incidence of venous thromboembolic or bleeding outcomes. Four were nested in randomized controlled trials^{56,68,73,117} while seven were controlled observational studies.¹³⁶⁻¹⁴¹ All four nested studies evaluated patients who had total hip replacement surgery (n=2469), one study evaluated patients who had total knee replacement surgery (n=1460), one study evaluated patients who had hip fracture surgery (n=5300), three studies evaluated patients who had either total knee or hip replacement surgery (n=2035) and two studies evaluated all three major orthopedic surgeries (n=9357). The most recent study was published in 2010 while the earliest was published in 1991. Four studies did not report funding source,^{137,139,140,150} two were funded by industry,^{136,138} and one was funded by academia and foundation.¹⁴¹

The mean age of patients ranged from 62.3 to 80 years.^{117,140} Females represented between 47.0 to 82.91 percent of the enrolled population.^{140,141} Mean weight was rarely reported and ranged from 71 to 83.9 kilograms.^{117,136} Five studies evaluated exclusively patients who had primary surgery^{68,73,136-138} while two evaluated revision surgery as well.^{56,117} Mean hospital length of stay was reported in three studies and ranged from 4.4 to 10 days.^{117,139,141} Other baseline and procedural characteristics were scarcely reported.

Outcome Evaluations

We qualitatively summarized the findings from our literature search of surgical and postsurgical characteristics which may predict or differentiate patient risk of venous thromboembolic or bleeding outcomes in contemporary practice according to covariate. The qualitative summarization of patient characteristics follows according to the outcome evaluated.

Surgical Characteristics

Anesthesia Regimens

Seven randomized controlled trials and two observational studies evaluated the anesthesia regimen used during major orthopedic surgery. One of the randomized controlled trials compared spinal anesthesia with epidural anesthesia¹⁹ while the other six trials and the two nested observational studies compared general anesthesia with regional anesthesia.^{20,24,30,32,34,56,73,197}

One randomized controlled trial by Farag and colleagues compared spinal versus epidural anesthesia in 38 patients who had total hip replacement surgery.¹⁹ All patients received bilateral antiembolism compression stockings while patients in the spinal anesthesia group also received prophylaxis with a low molecular weight heparin. Presence of deep vein thrombosis was assessed on days 3 and 10 postoperatively and there were no events at either time point.

Six randomized controlled trials compared general versus regional anesthesia in patients who had major orthopedic surgery.^{20,24,30,32,34,197} Two trials did not provide patients with mechanical or pharmacologic venous thromboembolism prophylaxis.^{32,34} The first of these trials by McKenzie and colleagues randomized 40 patients who had hip fracture surgery to receive general anesthesia or subarachnoid blockade. The incidence of deep vein thrombosis and of asymptomatic deep vein thrombosis was significantly higher in those who received general anesthesia as opposed to subarachnoid blockade (75 percent versus 40 percent, $p < 0.05$; 75 percent versus 25 percent, $p = 0.004$). No deep vein thromboses were symptomatic in the group that received general anesthesia while three symptomatic events occurred in the subarachnoid blockade group (0 percent versus 15 percent, $p = 0.230$). The second of these trials by Modig and colleagues randomized 30 patients who had total hip replacement surgery to receive general anesthesia versus epidural anesthesia.³⁴ There was no significant difference in the incidence of pulmonary embolism in the general versus epidural anesthesia groups 14 days after surgery (46.7 percent versus 13.3 percent, $p = 0.111$). Although there was no significant difference in the incidence of deep vein thrombosis in the regional versus general anesthesia groups (33.3 percent versus 73.3 percent, $p = 0.067$), significantly less patients had a proximal deep vein thrombosis defined as an isolated femoral or calf and femoral vein thrombosis (20 percent versus 73.3 percent, $p < 0.05$) or a distal deep vein thrombosis defined as an isolated calf or calf and femoral vein thrombosis (26.67 percent versus 73.3 percent, $p = 0.028$) in the regional versus general anesthesia group.

The remaining four trials that compared general with regional anesthesia allowed the use of mechanical or pharmacological prophylaxis for venous thromboembolism.^{20,24,30,197} The first trial by Williams-Russo and colleagues randomized 262 patients who had total knee replacement surgery to receive general versus epidural anesthesia.³⁰ All patients received elastic stockings on postoperative day 1 as well as pharmacologic prophylaxis based on physician preference, which was aspirin 325mg twice daily in the majority of cases (71.8 percent). However, some patients received warfarin prophylaxis and the investigators reported outcomes only for those patients who received aspirin. There was no significant difference in the incidence of deep vein thrombosis in the general versus epidural anesthesia groups (48 percent versus 40 percent, $p = 0.300$). All deep vein thromboses were distal in location. The second trial by Mitchell and colleagues randomized 72 patients who had total knee replacement surgery to receive general versus epidural anesthesia.²⁴ Additionally, male patients received aspirin 650mg twice daily while female patients received low dose warfarin prophylaxis. Investigators reported there was no significant difference in gender between the two groups, with the majority of enrolled subjects being male (62.5 percent). There was no significant difference in the incidence of proximal deep vein thrombosis between the general and regional anesthesia groups (63 percent versus 46 percent, $p = 0.256$). The third trial by Jorgensen and colleagues randomized 48 patients who had total knee replacement surgery to general anesthesia versus epidural anesthesia.²⁰ All patients also wore graded compression stockings. Significantly fewer patients had a deep vein thrombosis in the epidural anesthesia group versus the general anesthesia group (17.6 percent versus 59.1 percent, $p = 0.02$). When comparing general versus epidural anesthesia, there was no

significant difference in symptomatic deep vein thrombosis (9.1 percent versus 0 percent, $p=0.586$), asymptomatic deep vein thrombosis (50 percent versus 17.6 percent, $p=0.080$), proximal deep vein thrombosis (13.6 percent versus 5.9 percent, $p=0.795$) or distal deep vein thrombosis (45.5 percent versus 11.8 percent, $p=0.056$). A fourth trial by Planes and colleagues randomized 194 patients who had total hip replacement surgery to receive general anesthesia plus enoxaparin 40mg 12 hours prior to surgery, spinal anesthesia plus enoxaparin 20mg one hour after the onset of anesthesia, or spinal anesthesia with no immediate use of enoxaparin.¹⁹⁷ Patients in all three groups continued enoxaparin 40mg 12 hours after surgery and then daily thereafter. This study was not found to be very useful to this review as the general anesthesia group received enoxaparin using a different regiment as one spinal anesthesia group and the other spinal anesthesia group received no enoxaparin at all. No patients had symptoms of a pulmonary embolism. There was no significant difference in the incidence of proximal deep vein thrombosis between the three groups, respectively (6.5 percent, 6.6 percent, 6 percent, $p=0.993$). However, there was a significant difference in the incidence of distal deep vein thrombosis when comparing the three groups, respectively (0 percent, 5 percent, 11 percent, $p=0.007$) and when comparing general anesthesia plus immediate enoxaparin versus epidural anesthesia without immediate enoxaparin (0 percent versus 11 percent, $p=0.013$). Major bleeding was not significantly different between the three groups, respectively (3.2 percent, 1.6 percent, 1.5 percent, $p=0.764$) and there were no episodes of minor bleeding.

Two nested observational studies evaluated the impact of general versus regional anesthesia on the incidence of deep vein thrombosis. The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.⁷³ The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a multivariate regression model. Authors report that general anesthesia versus regional anesthesia significantly influenced the risk of deep vein thrombosis although they did not report the magnitude or direction of the effect. The second study was nested in a randomized controlled trial which compared low-dose warfarin with intermittent pneumatic compression in patients who had total hip arthroplasty.⁵⁶ Multivariate regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that the type of anesthesia did not significantly influence the incidence of deep vein thrombosis.

Cemented Arthroplasty

Three randomized controlled trials and three nested observational study evaluated aspects of cemented arthroplasty during total hip replacement surgery.^{21,22,26,68} The first trial evaluated 200 patients who had unilateral or bilateral primary total hip replacement surgery and were randomized to undergo cemented versus cementless arthroplasty.²¹ Patients who had bilateral surgery were randomized by knee, therefore outcomes were reported out of the number of knees operated on ($n=300$). No concurrent pharmacologic or mechanical prophylaxis was allowed. When comparing cemented versus cementless procedures, there was no significant difference in the rate of deep vein thrombosis (20.7 percent versus 27.3 percent, $p=0.654$), proximal deep vein thrombosis (12.7 percent versus 15.3 percent, $p=0.618$) or distal deep vein thrombosis (14.7 percent versus 20 percent, $p=0.286$). The second trial evaluated 250 patients who had unilateral

total hip replacement and randomized to receive cemented versus noncemented Mallory head prosthesis.²² The majority of patients received prophylaxis with aspirin (46.4 to 58.9 percent) although some patients received warfarin (28.8 to 43.5 percent), both (8.2 to 10.1 percent), or neither (0.0 to 4.1 percent). When comparing cemented arthroplasty to cementless arthroplasty, there was no significant difference in the rate of pulmonary embolism (2.4 percent versus 0.8 percent, $p=0.37$), deep vein thrombosis (50.0 percent versus 47.1 percent, $p=0.73$), proximal deep vein thrombosis (3.0 percent versus 4.8 percent, $p=0.67$) or distal deep vein thrombosis (50.0 percent versus 46.4 percent, $p=0.67$).

The third trial evaluated 130 patients who had primary total hip replacement surgery and were randomized to undergo the surgical procedure with a bone vacuum cementing technique versus a standard cementing technique.²⁶ All patients also received prophylaxis with the low molecular weight heparin nadroparin and bilateral thigh-high antithromboembolic stockings. There were no clinically suspected pulmonary emboli in the groups compared during the 45 day followup. There was a significantly lower rate of deep vein thrombosis in the group that received bone vacuum cementing versus standard cementing (3 percent versus 18 percent, $p=0.009$) as well as a significantly lower rate of proximal deep vein thrombosis (0 percent versus 11 percent, $p=0.020$). There was no difference in the rate of distal deep vein thrombosis between the intervention and control groups (3 percent versus 8 percent, $p=0.437$). This trial also evaluated major and minor bleeding. No major bleeding episodes occurred in the groups compared and the rate of minor bleeding was not significantly different between the intervention and control groups (8 percent versus 6 percent, $p=1.00$).

Three nested observational studies evaluated the impact of cemented prosthesis on the risk of deep vein thrombosis. The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to unfractionated heparin in patients who had total hip replacement surgery.⁶⁸ In the patients who received desirudin therapy, risk factors associated with the development of deep vein thrombosis were analyzed with multiple regression analysis and adjusted for peak partial thromboplastin time, age, gender, obesity, smoking habits and cemented surgery. Authors reported that cemented prosthesis had little to no influence on the risk of deep vein thrombosis although the magnitude or direction of effect was not reported. The second study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.⁷³ The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a multiple regression model. The authors reported that cemented versus noncemented prosthesis significantly influenced the risk of deep vein thrombosis ($p < 0.02$) although the magnitude and direction of the effect were not reported. The third study was nested in a randomized controlled trial which compared low-dose warfarin with intermittent pneumatic compression in patients who had total hip arthroplasty.⁵⁶ Multiple regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that the type of stem did not influence the incidence of deep vein thrombosis.

Tourniquet Use

Three randomized controlled trials evaluated aspects of tourniquet use during total knee replacement surgery.^{28,31,33} The first trial evaluated 80 patients who had primary, cemented total knee replacement surgery and were randomized to have a pneumatic tourniquet placed around the thigh and inflated versus a pneumatic tourniquet placed around the thigh but not inflated.³¹ All patients received prophylaxis with dalteparin as well. Four symptomatic deep vein thromboses, all femoral in location, occurred 8 to 21 days postoperatively in the group whose tourniquet was inflated while none occurred in the control group (10 percent versus 0 percent, $p=0.116$) although the difference was not significant. No distal deep vein thromboses occurred in the groups compared. In a second trial, 77 patients who also underwent cemented total knee replacement surgery were randomized to undergo surgery with an inflated tourniquet versus no tourniquet use.³³ One asymptomatic deep vein thrombosis in the popliteal vein was diagnosed during the postoperative ultrasound on day 10 in a patient who had surgery with the use of a tourniquet while none occurred in the control group (2.7 percent versus 0 percent, $p=0.481$) and this finding was not significant. No distal deep vein thrombosis occurred in the groups compared.

The third trial evaluated 20 patients who had bilateral cemented total knee replacement surgery with the use of a tourniquet. Within a patient, each knee was randomized to be operated on with tourniquet release and hemostasis prior to wound closure versus tourniquet release after wound closure and pressure dressing.²⁸ All patients also received low molecular weight heparin prophylaxis with nadroparin. No deep vein thromboses occurred in the groups compared.

Limb Positioning

Two randomized controlled trials evaluated variations of limb position during major orthopedic surgery.^{18,29} The first trial evaluated 118 patients who had primary, cemented total knee replacement and were randomized to two groups.²⁹ The intervention group underwent the surgical procedure with a time limit for flexion and dislocation of the knee in order to minimize the total time the knee was in extreme flexion. The control group underwent the surgical procedure with the knee maintained in flexion and dislocation for the duration of the surgery. All patients received aspirin postoperatively for venous thromboembolism prophylaxis and the outcomes were reported out of the number of knees operated on. There was no significant difference in the rate of deep vein thrombosis between the intervention and control group (38 percent versus 42 percent, $p=0.60$) or in the rate of proximal deep vein thrombosis between the intervention and control groups (16 percent versus 12 percent, $p=0.40$).

The second trial evaluated 160 patients who had primary, cemented total hip replacement surgery and were randomized into two groups.¹⁸ The intervention group underwent the surgical procedure in a modified position to maintain femoral blood flow monitored with ultrasound whereas the control group underwent the surgical procedure without femoral blood flow monitoring in a full figure-of-four positioning of the leg. All patients received prophylaxis with the low molecular weight heparin nadroparin and customized anti-thrombosis stockings. No clinically suspected pulmonary emboli occurred in the groups compared. There was no significant difference in the rate of symptomatic deep vein thrombosis between the intervention and control groups (0 percent versus 4 percent, $p > 0.05$). All deep vein thrombosis occurred in patients who were in the control group, one of which was femoral, one in the lower leg, and one patient had involvement of the popliteal vein and lower leg.

Tissue Fibrin Adhesive

One randomized controlled trial evaluated 58 patients who had unilateral, cemented, total knee replacement surgery and randomized patients to receive treatment with tissue fibrin adhesive (Octacol F15) versus standard methods of hemostasis.²³ All patients received enoxaparin 40mg subcutaneously every 12 hours prior to surgery and then every 12 hours after surgery. This trial did not report any bleeding outcomes of interest. No patients developed an ultrasound confirmed deep vein thrombosis and one patient in the control group suffered from a fatal pulmonary embolism while none occurred in the group that received tissue fibrin adhesive (3.5 percent versus 0 percent, $p=1.00$).

Primary or Revision Surgery, Perioperative Blood Loss, Operative Time, and Blood Transfusions

One nested observational study evaluated the impact of additional surgical characteristics on their impact on the incidence of deep vein thrombosis. This study was nested in a randomized controlled trial which compared low-dose warfarin with intermittent pneumatic compression in patients who had total hip arthroplasty.⁵⁶ Multiple regression analysis was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that revision versus primary surgery significantly influenced the incidence of deep vein thrombosis although perioperative blood loss, operative time, and blood transfusions did not.

Patient Characteristics

Symptomatic Objectively Confirmed Venous Thromboembolism

Three controlled observational studies evaluated the impact of patient specific characteristics on the incidence of symptomatic objectively confirmed venous thromboembolism.^{136,138,140} The first study by Dorr and colleagues evaluated patients who had total hip or knee replacement surgery and compared patients who were considered high risk to those considered low risk to evaluate the incidence of thromboembolism.¹³⁶ Low risk was defined as having none or at least one of the following: congestive heart failure, prior deep vein thrombosis more than 5 years ago, inactive malignant disease, current use of hormone replacement therapy, chronic tobacco use, blood disorders of the sickle-cell trait, polycythemia vera or thrombocytopenia. Within the low risk group, multivariate analysis of the risk factors for symptomatic objectively confirmed venous thromboembolism, adjusted for age was conducted. Congestive heart failure [adjusted odds ratio (AOR) 7.7, $p=0.0001$], inactive malignant disease (AOR 3.1, $p=0.014$), and hormone replacement therapy (AOR 3.2, $p=0.008$) increased the odds of symptomatic objectively confirmed venous thromboembolism. Authors reported that age was not a significant risk factor in the analysis and did not evaluate the high risk subgroup for risk factors for symptomatic objectively confirmed venous thromboembolism. The second study by McNamara and colleagues evaluated patients who had hip fracture surgery and compared patients with and without symptomatic objectively confirmed venous thromboembolism to assess for risk factors.¹⁴⁰ Multivariate analysis adjusted for age, gender, residence on admission (own home versus institution), mean hemoglobin on admission and type of fracture (intracapsular, intertrochanteric, subtrochanteric) showed that patients who lived in their own home [AOR 2.24 (1.32 to 3.82), $p=0.003$], those who presented with intertrochanteric fractures [AOR 2.15 (1.46 to

3.17), $p=0.001$] or subtrochanteric fractures [AOR 1.51 (0.53 to 4.30), $p=0.001$], or those with elevated hemoglobin on admission [AOR 1.01 (1.0 to 1.03, $p=0.01$] had an increased odds of symptomatic objectively confirmed venous thromboembolism. Male gender [AOR 0.64 (0.38 to 1.07), $p=0.09$] and age [AOR 1.0 (0.98 to 1.02), $p=0.9$] did not significantly impact the risk of symptomatic objectively confirmed venous thromboembolism. The third study by Liezorovicz and colleagues evaluated Asian patients who had total hip or knee replacement surgery or hip fracture surgery and compared patients with or without the primary outcome to evaluate for risk factors.¹³⁸ The primary outcome was symptomatic objectively confirmed venous thromboembolism or sudden death at hospital discharge. Upon multivariate analysis adjusted for age, personal or familial history of venous thromboembolism, history of cancer or active cancer, varicose veins and chronic heart failure, personal or familial history of venous thromboembolism [AOR 26.9 (2.9 to 250.1)], chronic heart failure [AOR 5.1 (1.5 to 17.8)] and varicose veins [AOR 3.6 (1.2 to 10.6)] were significant independent risk factors for the primary outcome. At the 1 month followup, personal or familial history of venous thromboembolism [AOR 18.1 (2.0 to 167.0)] and chronic heart failure [AOR 6.3 (2.1 to 18.6)] remained significant predictors of the primary outcome.

Pulmonary Embolism

One nested case-controlled observational study evaluated the impact of patient specific characteristics on the incidence of pulmonary embolism.¹³⁹ This study by Lemos and colleagues evaluated patients who received warfarin prophylaxis as part of a larger trial and underwent total knee or hip replacement surgery. Patients with pulmonary embolism were compared with gender and procedure-matched controls without pulmonary embolism to determine risk factors for pulmonary embolism. Upon multivariate analysis, factors that increased the risk of pulmonary embolism included advancing age ($p=0.008$) and genitourinary infection ($p=0.017$) while the presence of cardiovascular disease decreased the risk of pulmonary embolism ($p=0.011$). History of phlebitis, use of thyroid replacement medication, history of pulmonary embolism, varicosities, phlebitis in the opposite extremity, or peripheral vascular disease were not found to be significant factors.

Deep Vein Thrombosis

Four observational studies evaluated the impact of patient characteristics on the incidence of deep vein thrombosis.^{56,68,73,141} Three studies were nested within randomized controlled trials which compared different pharmacologic prophylaxis regimens.^{56,68,73} The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.⁷³ The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a logistic regression model. The patient characteristics significantly influenced the risk of deep vein thrombosis, including age ($p < 0.001$) and presence of obesity ($p < 0.01$). The second study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to unfractionated heparin in patients who had total hip replacement surgery.⁶⁸ In the patients who received desirudin therapy, risk factors associated with the development of deep vein thrombosis were analyzed with multiple regression analysis and adjusted for peak partial thromboplastin time, age, gender, obesity, smoking habits and cemented surgery. Patients over the age of 65 and females were at increased risk of deep vein thrombosis ($p < 0.01$ for each) and obesity was not a significant risk factor ($p > 0.2$). Authors also reported

that smoking had little to no influence on the risk of deep vein thrombosis. The third study was nested in a randomized controlled trial which compared low-dose warfarin with intermittent pneumatic compression in patients who had total hip arthroplasty.⁵⁶ Logistic regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that aside from the treatment regimen, none of the patient characteristics (age, gender, height, and weight) significantly influenced the incidence of deep vein thrombosis.

One controlled observational study evaluated the impact of the factor V Leiden mutation on the incidence of deep vein thrombosis.¹⁴¹ Logistic regression analysis adjusted for the presence of factor V Leiden mutation, surgical site, anticoagulant prophylaxis, and medical center. This study showed that factor V Leiden mutation did not significantly contribute to the risk of deep vein thrombosis.

Proximal Deep Vein Thrombosis

Two controlled observational studies evaluated the impact of patient specific characteristics on the incidence of proximal deep vein thrombosis.^{117,136} The first study by Dorr and colleagues evaluated patients who had total hip or knee replacement surgery and compared patients who were considered high risk with those considered low risk to evaluate the incidence of thromboembolism.¹³⁶ Low risk was defined as having none or at least one of the following: congestive heart failure, prior deep vein thrombosis more than 5 years ago, inactive malignant disease, current use of hormone replacement therapy, chronic tobacco use, blood disorders of the sickle-cell trait, polycythemia vera, or thrombocytopenia. Within the low risk group, multivariate analysis of the risk factors for proximal deep vein thrombosis, adjusted for age and the listed risk factors was conducted. Only the presence of congestive heart failure (AOR 6.2, p=0.0005) increased the odds of proximal deep vein thrombosis. The second study was nested in a randomized controlled trial which compared intermittent pneumatic compression alone or in combination with aspirin or warfarin in patients who had total hip replacement surgery.¹¹⁷ Authors report that upon multiple regression analysis for the presence of proximal deep vein thrombosis adjusted for age, history of deep vein thrombosis, or revision surgery that age was a significant risk factor although the magnitude and direction of effect were not reported.

Symptomatic Deep Vein Thrombosis

One controlled observational study evaluated patients who had total knee replacement to determine if the presence of metabolic syndrome impacted the incidence of symptomatic deep vein thrombosis.¹³⁷ Multivariate analysis adjusted for age, gender, education, body mass index, Charlson index, diabetes, hypertension, hypercholesterolemia, and metabolic syndrome showed that metabolic syndrome increased the odds of symptomatic deep vein thrombosis [AOR 3.0 (1.1 to 12.4)]. Age [AOR 0.9 (0.87 to 1.0)], gender [AOR 3.4 (0.4 to 18.5)], education [AOR 4.1 (0.8 to 20.6)], diabetes [AOR 3.1 (0.4 to 21.9)], hypertension [AOR 2.3 (0.6 to 32.2)], hypercholesterolemia [AOR 1.6 (0.2 to 33.5)], body mass index [AOR 1.1 (0.9 to 1.3)], and comorbidity [AOR 1.3 (0.9 to 2.2)] did not significantly impact the odds of proximal deep vein thrombosis.

Major Bleeding

One controlled observational study evaluated patients who had total knee or hip replacement or hip fracture surgery and whether age, gender, obesity, risk of bleeding, specific surgery, or type of prophylaxis administered affected the risk of major bleeding.¹⁵⁰ All characteristics were suggested to significantly impact the risk of major bleeding except obesity, although the magnitude and direction of effect were not reported.

Strength of Evidence and Applicability of the Body of Evidence

Key Question 2 evaluated the impact of patient, surgical or postsurgical characteristics on outcomes of interest. Overall data were insufficient for all patient characteristics with the exception of two; congestive heart failure and age. There was moderate strength of evidence that congestive heart failure increased the odds of symptomatic objectively confirmed venous thromboembolism and there was low strength of evidence that age did not impact the odds of symptomatic objectively confirmed venous thromboembolism and increased the odds of deep vein thrombosis, in major orthopedic surgery. Similarly, data were insufficient for all surgical or postsurgical characteristics with the exception of two comparisons; general versus regional anesthesia and cemented versus noncemented arthroplasty. There was low strength of evidence that patients who had general anesthesia had a higher risk of deep vein thrombosis compared with regional anesthesia while there was no difference in the risk of proximal or distal deep vein thrombosis compared with regional anesthesia. There was also low strength of evidence that patients who had cemented arthroplasty had no difference in the risk of deep vein thrombosis or proximal deep vein thrombosis compared with noncemented arthroplasty.

In Key Question 2, surgical characteristics were rated with low applicability because the majority of trials were conducted outside of the United States, had shorter duration of followup to adequately evaluate the outcomes of interest, and often represented one of the three major orthopedic surgeries but not all. Additionally, for comparisons of general versus regional anesthesia, many trials used anesthetics that are not currently available on the U.S. market. Patient characteristics were rated low to moderate in applicability. Limitations included the country in which studies were conducted and representation of the three major orthopedic surgeries. Many patient characteristics are not applicable to hip fracture surgery as few studies included this surgical population.

Key Question 3

In patients undergoing major orthopedic surgery (total hip replacement, total knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?

Key Points

- There were no reliable data concerning the relationship between final health outcomes other than pulmonary embolism and the occurrence of deep venous thrombosis in patients undergoing major orthopedic surgery.

- No trials or studies were available assessing whether deep venous thrombosis was correlated with or a multivariate predictor of pulmonary embolism in patients undergoing major orthopedic surgery.
- In the available studies, the routine use of prophylaxis reduced the occurrence rate of deep venous thrombosis and the scheduled anticoagulant treatment for deep venous thrombosis once it was detected may have diminished the number that developed into pulmonary embolism.
- In one observational study in total knee replacement surgery, the overall occurrence of pulmonary embolism and the subset with symptomatic pulmonary embolism occurred more frequently in those with deep venous thromboses. However the data were not adjusted for confounders and we could not discern whether these things are correlated or collinear.
- The available clinical trials provided insufficient data to determine the association between deep venous thrombosis and pulmonary embolism in major orthopedic surgery.

Detailed Analysis

Study Design and Characteristics

Eight randomized controlled trials (N=2114) and two controlled observational studies (N=2299) evaluated the relationship between surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) and patient important outcomes in patients undergoing major orthopedic surgery.^{20,85,110,114,115,117,132,134,142,143} However, none of the trials and only one observational study was designed to evaluate the relationship between surrogate and patient important outcomes.¹⁴² All eight randomized controlled trials were published as full text manuscripts. The first trial compared injectable low molecular weight heparin with combination of injectable low molecular weight heparin and mechanical prophylaxis.¹¹⁴ The second trial compared injectable low molecular weight heparin agents with oral vitamin K antagonists.⁸⁵ The third trial compared oral antiplatelet agents with a combination of oral antiplatelet agents and mechanical prophylaxis.¹¹⁵ The fourth trial reported comparisons between injectable unfractionated heparin, mechanical prophylaxis and combination of both these modalities.¹³⁴ The fifth trial compared mechanical prophylaxis with a combination of mechanical and oral vitamin K antagonists.¹¹⁷ The sixth trial reported comparisons between oral vitamin K antagonists, oral antiplatelet agents and placebo.¹³² The seventh trial compared two intermittent pneumatic compression devices.¹¹⁰ The eighth trial compared general with epidural anesthesia.²⁰ Three trials enrolled patients who had total hip replacement surgery (N=502),^{115,117,134} three trials enrolled patients who had total knee replacement surgery (N=1141),^{20,85,110} one trial enrolled patients with either total hip replacement or total knee replacement surgery,¹¹⁴ and one trial enrolled patients who had hip fracture surgery (N=194).¹³² The earliest trial was published in 1989¹³² and the most recent trial was published in 2008.¹¹⁴ The duration of followup ranged from postoperative period to 180 days. Four trials received funding from the industry,^{20,85,110,114} one trial received funding from industry and government,¹³² two trials were unfunded^{115,117} and in one trial funding source was not reported.¹³⁴

The mean age of enrolled patients ranged from 62.3 years to 76.6 year.^{117,132} Females represented between 50.0 and 81.0 percent of the enrolled populations.^{117,132} The mean weight ranged from 71.0 to 88.0 kilograms.^{114,117} Few patients enrolled had a history of venous thromboembolism ranging from 0.0 to 14.0 percent.^{20,114,115,117} Two trials reported presence of

varicosity ranging from 7.0 to 14.0 percent.^{20,117} One trial reported the percent of patients with a history of malignancy ranging from 15.6 to 18.6 percent.¹¹⁴

Sixty eight to 100 percent of patients underwent primary surgery.^{115,117,134} The percent of patients who had cemented fixation during surgery ranged from 0.0 to 89.2 percent.^{85,134} Mean duration of surgery ranged from 86.0 to 126.2 minutes^{85,115} and the mean duration of anesthesia was not reported. One trial directly compared general with epidural anesthesia.²⁰ Otherwise, the use of general anesthesia was reported by three trials and ranged from 12.0 to 87.2 percent of patients.^{85,110,134} Four trials reported regional anesthesia use which ranged from 12.8 to 100 percent of patients.^{85,110,115,134} One trial reported combination of general and regional anesthesia ranging from 0.46 to 0.49 percent.¹¹⁰ The mean length of hospital stay was reported by two trials ranging from 3 to 10 days.^{114,117}

Of the two controlled observational studies one study (N=1257), published in 1992, compared patients who had total knee arthroplasty with and without calf thrombi to compare the risk of pulmonary embolism.¹⁴² The second study (N=1042), published in 1997, evaluated patients who had total hip replacement surgery for the development of pulmonary embolism before and after discharge along with complications of low-dose warfarin use. One study did not report the funding source¹⁴² while the other study reported being unfunded.¹⁴³

Baseline and procedural characteristics of the patients enrolled in these studies were scarcely reported. One study reported the average age of patients was 59 years, 61.87 percent of the surgeries were primary, 2.13 percent of patients had a history of venous thromboembolism and the average duration of hospitalization was 11 days.¹⁴³ The other study did not report specific baseline or procedural characteristics.¹⁴²

Outcome Evaluations

Given the paucity of data that were available to answer this Key Question and the fact that we did not statistically pool any trials or studies in this Key Question, we allowed outcomes (such as deep venous thromboses and pulmonary embolism) that were not as clearly defined or defined using tests that would not otherwise fit our methodology.

Total Knee Arthroplasty

The most compelling evaluation of the link between deep venous thrombosis and pulmonary embolism was an observational study of 1257 patients (having 1625 total knee arthroplasty surgeries) undergoing total knee arthroplasty surgery at one hospital in the United States between 1974 and 1986.¹⁴² Patients in this study had preoperative and postoperative perfusion lung scans and postoperative venograms per standard hospital practice. Those found to have calf thrombi (asymptomatic or symptomatic), asymptomatic proximal thrombi or asymptomatic lung scans were treated with warfarin to maintain prothrombin 1.3 to 1.6 times control. Patients diagnosed with large or symptomatic proximal thrombi or symptomatic pulmonary emboli were treated with intravenous heparin followed by warfarin for six months. There were positive lung scans for pulmonary embolism (symptomatic and asymptomatic) in 6.9 percent of patients with calf thrombi versus 2.0 percent of patients without calf thrombi ($p<0.001$). Symptomatic pulmonary embolism occurred in 1.6 percent of patients with calf thrombi versus 0.2 percent of patients with negative venograms ($p=0.034$). When patients with proximal thrombi were compared against those with no thrombi, 4.8 percent versus 2.0 percent ($p=NS$) had pulmonary embolism and 1.9 percent versus 0.2 percent ($p=NS$) had symptomatic pulmonary embolism.

Four trials evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after undergoing total knee arthroplasty. In the first trial, 417 patients

undergoing total knee arthroplasty received either warfarin or enoxaparin prophylaxis.⁸⁵ Venography was done on postoperative day 14 or earlier if the patient was to be discharged or had suspected deep venous thrombosis via ultrasonography or impedance plethysmography. Patients who were diagnosed with venous thromboembolism were treated with heparin followed by oral anticoagulants as per local practice. Overall, 185 patients developed a deep vein thrombosis of which 46 were proximal. Four patients developed pulmonary embolism with the three of the patients not having venography and one of these patients having a normal ultrasonography evaluation. The fourth patient had bilateral deep venous thromboses in both calves. In the second trial, 153 patients had total knee arthroplasty and received a low molecular weight heparin with or without a leg mechanical compression device.¹¹⁴ Patients received a duplex ultrasound of the legs before discharge and were followed up for 3 months for signs and symptoms of pulmonary embolism. Treatment of positive venous thromboembolic findings was not described. From this group, 19 had deep venous thrombosis (12.4 percent) of which one had developed a distal deep venous thrombosis detected by ultrasound at discharge and subsequently developed a pulmonary embolism 29 days later. Another patient with a negative ultrasound for deep venous thrombosis developed pulmonary embolism on postoperative day 2. In the third trial, 423 patients undergoing total knee arthroplasty received one of two pneumatic compression devices for prophylaxis.¹¹⁰ Ultrasonography of the calf and thigh was performed 3-5 days after the operation and when symptoms of deep venous thrombosis were detected. Spiral computed tomography was used to detect pulmonary embolism in symptomatic patients. Patients diagnosed with femoral or proximal popliteal thrombi were treated with either heparin or low molecular weight heparin followed by warfarin for three months. In this trial, 52 of 423 patients (12.3 percent) had deep venous thrombosis of which one patient (0.2 percent) developed pulmonary embolism. In this patient, the routine ultrasonography on the fourth postoperative day was negative for thrombi but a repeat test on day twelve was positive. No other pulmonary emboli occurred during the trial. In the fourth trial, 48 patients who had primary or revision knee arthroplasty were randomized to receive either general or epidural anesthesia. No pharmacologic prophylaxis was administered but all patients wore thigh-length compression stockings.²⁰ All patients were screened on day 9-11 for deep vein thrombosis with bilateral ascending venography. Treatment of positive venous thromboembolic findings was not described. A total of 16 patients developed a deep vein thrombosis, 13 in the general anesthesia group and three in the epidural anesthesia group. One patient with deep vein thrombosis confined to the lower leg in the general anesthesia group developed a nonfatal pulmonary embolism (confirmed with ventilation-perfusion scan) on postoperative day five.

Total hip Arthroplasty

An observational study of 1042 patients (1244 hips) was conducted at a single medical center in the United States between 1987 and 1993.¹⁴³ All patients received prophylaxis with low dose warfarin (goal prothrombin time between 14 and 17 seconds). Followup continued for three months in this study but they did not define the monitoring schedule to determine the occurrence of pulmonary embolism or deep venous thrombosis. It appears that the investigators only scanned for deep venous thrombosis of pulmonary embolism when the patients had symptomatic complaints. Those diagnosed with proximal thrombi were treated with intravenous heparin followed by warfarin for three months while patients with distal thrombi were treated with warfarin only. Five total hip arthroplasties were followed by the development of symptomatic deep venous thrombosis (0.5 percent of hips). Four were proximal deep venous thromboses and one was distal, as confirmed by venography or ultrasonography. Three of the five hips (60

percent) with deep venous thrombosis occurred in patients who concurrently or subsequently developed pulmonary embolism. Overall, 12 total hip arthroplasties, including the three described above, resulted in symptomatic pulmonary embolism and 10 of 12 were diagnosed with a ventilation perfusion scan.

Four trials evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after total hip arthroplasty. In the first trial, 30 patients undergoing hip replacement surgery did not receive pharmacologic or mechanical prophylaxis but were randomized to receive general versus epidural anesthesia.³⁴ Bilateral venography was conducted 14 days prior to and after surgery in all patients as was perfusion lung scanning and chest radiography. Treatment of positive venous thromboembolic findings was not described. A total of 16 patients (53.3 percent) developed a deep vein thrombosis, 11 in the general anesthesia group (36.7 percent) and five in the epidural anesthesia group (33.3 percent). Nine of the patients with a deep vein thrombosis (56.3 percent) were diagnosed with a pulmonary embolism [seven in the general anesthesia group (63.6 percent) and two in the epidural anesthesia group (40 percent)]. In the second trial 231 patients had total hip arthroplasty (a total of 250 hips) and received aspirin with or without a pneumatic compression boot.¹¹⁵ Patients received venography of the thigh or calf on the sixth, seventh, or eighth postoperative days. Patients diagnosed with a deep vein thrombosis were treated with warfarin for three months. One proximal thrombus (popliteal vein), 15 distal thrombi, and two pulmonary emboli occurred. The patients with pulmonary emboli had negative venograms before discharge but late pulmonary embolism approximately 3 weeks postoperatively. In the third trial, 75 patients undergoing total hip arthroplasty received heparin with aspirin, pneumatic pump compression, or both strategies.¹³⁴ Duplex ultrasonography was conducted at baseline, 1 and 2 weeks after surgery with venograms confirming positive results. Patients diagnosed with a deep vein thrombosis were treated with heparin and warfarin. Five of the patients developed deep venous thrombosis, three patients were symptomatic, two were asymptomatic, and one developed pulmonary embolism. No pulmonary embolism was found aside for the patient with deep venous thrombosis. In the fourth trial, 212 patients (217 hips) undergoing total hip arthroplasty received pneumatic compression alone, with aspirin, or with warfarin.¹¹⁷ Venography, ultrasonography, or both were conducted just before the patient was about to be discharged (4 to 13 days postoperatively). Patients diagnosed with a proximal thrombus were treated heparin, warfarin or both and patients diagnosed with calf thrombi were treated with warfarin if they were symptomatic. Twenty-two of the 217 arthroplasties (10.1 percent) resulted in deep venous thrombosis. The only pulmonary embolism occurred in a patient who also had a deep venous thrombosis detected by ultrasonography of the thigh.

Hip Fracture Surgery

One trial evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after hip fracture surgery. In one trial, 194 patients undergoing hip fracture surgery received warfarin, aspirin, or placebo.¹³² Patients had venography on day 21 or at the time of discharge. Venography was performed sooner if an iodine fibrinogen leg scan or impedance plethysmography was found to be positive. Patients diagnosed with a deep vein thrombosis were treated with intravenous heparin followed by oral anticoagulation therapy. Sixty nine patients developed deep venous thrombosis or pulmonary embolism. Of the three patients with pulmonary embolism, one patient developed a deep venous thrombosis on postoperative day 10, was not treated with heparin but discharged and died of autopsy reported pulmonary embolism on day 20. Another patient had a positive impedance plethysmography test and pulmonary

embolism on day 14 but the venogram was said to be inadequate while the final patient had a pulmonary embolism on day seven with a calf vein thrombus found in the left leg on day 10.

Strength of Evidence and Applicability of the Body of Evidence

There was insufficient evidence to determine the relationship between deep vein thrombosis and pulmonary embolism. Key Question 3 had moderate applicability as most of the data were derived from trials and studies conducted in the United States and within the 1990's although two limitations were that the majority of data were in knee replacement surgery with little from hip fracture surgery and the duration of followup is generically stated as postoperative in the majority of trials.

Key Question 4

In patients who had major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism-related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep vein thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to re-operation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, re-admission, and re-operation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump)].

Key Points

Pharmacologic Prophylaxis

- There is a high level of evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases the occurrence of proximal deep vein thrombosis [RR 0.53 (0.39 to 0.74)] and distal deep vein thrombosis [RR 0.59 (0.42 to 0.82)] while significantly increasing minor bleeding [RR 1.67 (1.18 to 2.38)].
 - The analyses of deep vein thrombosis have higher levels of heterogeneity; this is likely due in part, to the inclusion of trials evaluating multiple classes of pharmacologic therapy within the analysis and the inclusion of trials that were published prior to 2001 within the analysis.
- There is a moderate level of evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases the occurrence of deep vein thrombosis [RR 0.56 (0.47 to 0.68)] and asymptomatic deep vein thrombosis [RR 0.52 (0.40 to 0.69)].
- There is a low level of evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major venous thromboembolism [RR 0.21 (0.05 to 0.95)].

- Pharmacologic prophylaxis did not significantly impact the occurrence of symptomatic objectively confirmed venous thromboembolism although this was based on a single randomized controlled trial.
- Pharmacologic prophylaxis did not significantly impact pulmonary embolism in the base case analysis but did significantly reduce the risk of pulmonary embolism in the trials not allowing any background prophylaxis in both groups.
- Pharmacologic prophylaxis versus no prophylaxis did not significantly impact nonfatal pulmonary embolism, mortality, symptomatic deep vein thrombosis or major bleeding in patients undergoing major orthopedic surgery.
- No clinical trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on reoperation and readmission. A single observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on reoperation and readmission. Pharmacologic prophylaxis increased reoperation but did not impact readmission.
- Pharmacologic prophylaxis versus no prophylaxis did not significantly impact fatal pulmonary embolism, mortality due to bleeding, major bleeding leading to reoperation and bleeding leading to transfusion in patients undergoing major orthopedic surgery, however the impact is based on the results of a single trial for each endpoint because the rest of the trials evaluating these endpoints reported no events in the two comparative groups.
- No data are available to evaluate the comparative effect of pharmacologic prophylaxis versus no prophylaxis on post thrombotic syndrome, health related quality of life, surgical site bleeding, bleeding leading to infection, heparin induced thrombocytopenia and discomfort in patients undergoing major orthopedic surgery.

Mechanical Prophylaxis

- One randomized controlled trial showed that mechanical prophylaxis versus no prophylaxis significantly decreased deep vein thrombosis in patients undergoing major orthopedic surgery.
- Mechanical prophylaxis versus no prophylaxis does not significantly impact proximal deep vein thrombosis or distal deep vein thrombosis in patients undergoing major orthopedic surgery.
- No data are available to evaluate the comparative effect of mechanical prophylaxis versus no prophylaxis on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, post thrombotic syndrome, mortality, mortality due to bleeding, health related quality of life, asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, reoperation and readmission in patients undergoing major orthopedic surgery.
- The comparative impact of mechanical prophylaxis versus no prophylaxis on pulmonary embolism, fatal pulmonary embolism and nonfatal pulmonary embolism could not be determined since no events occurred in the two comparative groups in the available trials.

Detailed Analysis

Study Design and Characteristics

Twenty randomized controlled trials (N=2868) and three controlled observational studies (N=12866) evaluated the impact of combined pharmacologic and mechanical modalities versus no thromboprophylaxis on final health, intermediate and adverse outcomes.^{35-38,40-45,47,49-53,132,133,135,144,146,150}

All 20 randomized controlled trials were published as full text manuscripts.

One full text manuscript included two independent randomized controlled trials.³⁸ Eighteen randomized controlled trials compared pharmacologic prophylaxis to no prophylaxis,^{35,36,38,40-45,47,49,50,52,53,132,133,135}

and of these 11 compared pharmacologic prophylaxis with a truly no prophylaxis.^{35,36,40,43,47,49-51,132,133} Two randomized controlled trials compared mechanical prophylaxis with no prophylaxis^{37,51} and of these one compared mechanical prophylaxis with truly no prophylaxis.⁵¹ To qualify as being “truly no prophylaxis” the trials had to compare pharmacologic or mechanical prophylaxis with placebo or no prophylaxis without the use of any concurrent prophylaxis in the groups compared; whereas in the broader category of studies comparing pharmacologic or mechanical prophylaxis versus placebo or no prophylaxis along with concurrent use of graduated compression stockings in the groups compared were also included. Fourteen trials exclusively enrolled patients who had total hip replacement surgery (N=2069),^{35,37,38,41,42,44,45,47,49,50,52,53,133,135} four trials enrolled patients who had total knee replacement surgery (N=537),^{36,38,43,51} and two trials enrolled patients who had hip fracture surgery (N=262).^{40,132} The earliest trial was published in 1980 while the most recent published in 2011.^{43,135} The duration of followup ranged from the postoperative period to 90 days. Four trials received funding from industry,^{38,53,133} two trials received funding from government and foundation,^{49,50} one trial received funding from industry and government,¹³² two trials received funding from government,^{35,52} one trial did not receive funding from any commercial party,³⁷ and in nine trials the funding source was not reported.^{36,40-42,44,45,47,51,135}

The mean age of enrolled patients ranged from 60.6 to years to 79 years. Females represented between 18.0 to 91.82 percent of the enrolled populations. The mean weight ranged from 54.2 to 74.0 kilograms with only one trial reporting obesity which ranged from 21.43 to 59.4 percent. Few patients enrolled had a history of venous thromboembolism, with the majority of trials reporting 0 to 10.0 percent. Presence of varicosity was ranged from no varicosity to 55.0 percent. The percent of patients with a history of malignancy ranged from 0.0 to 7.1 percent. None of the trials reported the percent of patients who had previously undergone orthopedic surgery.

Seventy-six to 100.0 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 0.0 to 100.0. Mean duration of surgery ranged from 57.0 to 139.2 minutes and the mean duration of anesthesia was only reported by one trial with 104.5 minutes as the mean duration for the intervention group and 112.6 minutes as the mean duration for the control group. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 7.69 to 100.0 percent of patients and regional anesthesia use ranging from 0.0 to 45.0 percent of patients. The mean length of hospital stay was infrequently reported, and when it was ranged from 7.9 to 16.0 days.

Three controlled observational studies (N=12866) evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery.^{144,146,150} All studies were published as full text manuscripts. Two studies compared patients who received warfarin versus no prophylaxis^{144,146} while one study also compared patients who received aspirin versus no prophylaxis.¹⁴⁴ The third study compared multiple regimens although the only

comparison which fit our inclusion criteria was between enoxaparin and no prophylaxis.¹⁵⁰ One study reported the outcomes separately for total hip replacement (N=2203) and then for total knee replacement (N=2050).¹⁴⁴ The second trial was limited to total knee replacement (N=1742).¹⁴⁶ The third trial collectively reported total hip replacement, knee replacement and hip fracture surgery.¹⁵⁰ The studies were published in 2010, 2009, and 2003.. The duration of followup for one study was until discharge¹⁵⁰ while the other two studies was 90 days.^{144,146} One trial was unfunded¹⁴⁶ while the other two did not disclose the funding source.^{144,150}

The mean age of patients ranged from 68 to 71 years. Other baseline characteristics were not reported in these studies. The majority of patients underwent primary surgery. One study reported the surgical approach. For patients who had total hip replacement, the posterior approach was used while for the patients who had total knee replacement the medial parapatellar approach was used.¹⁴⁴ One study reported the mean hospital length of stay of 15.8 days.¹⁵⁰ Other procedural characteristics as well as the mean hospital length of stay were not reported in these studies.

Outcome Evaluations

A summary of the results for Key Question 4 is presented in Table 10.

Symptomatic Objectively Confirmed Venous Thromboembolism

Pharmacologic Prophylaxis Versus no Prophylaxis

One randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.¹³⁵ This trial evaluated patients who had total hip replacement and included two separate comparisons: low molecular weight heparin (enoxaparin) versus placebo and injectable factor Xa inhibitor (fondaparinux) versus placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. No patients in the enoxaparin or placebo groups had an event therefore the risk of symptomatic thromboembolism could not be calculated for this comparison. In patients who received fondaparinux versus placebo, the odds of symptomatic venous thromboembolism were not significantly different [OR 7.30 (0.14 to 368.00)]. Subgroup analyses were not possible because only one comparison was available. No randomized controlled trials evaluated the impact of prophylaxis with oral antiplatelet agents, unfractionated heparin, or vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Major Venous Thromboembolism

Pharmacologic Prophylaxis Versus no Prophylaxis

One randomized controlled trial by Fuji and colleagues in 2010 evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major venous thromboembolism in patients who had major orthopedic surgery.⁵³ This trial evaluated patients who had total knee replacement

and included two separate comparisons of an oral direct thrombin inhibitor; dabigatran 150mg (mg) daily and dabigatran 220mg daily versus placebo. The use of concurrent elastic stockings was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major venous thromboembolism was significantly decreased [relative risk (RR) 0.21 (0.05 to 0.95), number needed to treat (NNT) 19 to 22] (Appendix G Figure 1). Statistical heterogeneity and publication bias could not be calculated because there were too few comparisons.

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of prophylaxis with oral antiplatelet agents, injectable low molecular weight heparins, unfractionated heparin, injectable or oral factor Xa inhibitors, or vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on this outcome.

Pulmonary Embolism

Pharmacologic Prophylaxis Versus no Prophylaxis

Twelve randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.^{35,36,38,42,44,49,50,52,53,132,135} The three trials by Fuji and colleagues each included two separate comparisons, as did the trials by Powers, Alfaro, and Yokote and colleagues.^{35,38,53,132,135} The trials by Fuji and colleagues in 2010, Samama and colleagues and Yokote and colleagues were excluded from the analysis because no events occurred in either group, as was one comparison from one of the trials by Fuji and colleagues in 2008. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.38 (0.13 to 1.07)] (Appendix G Figure 2). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.063).

When limiting the original analysis to trials that compared pharmacologic prophylaxis with truly no prophylaxis, five trials remained with the trials by Alfaro and Powers and colleagues each including two separate comparisons.^{35,36,49,50,132} In patients who received pharmacologic prophylaxis versus truly no prophylaxis the risk of pulmonary embolism was significantly decreased [RR 0.30 (0.09 to 0.99), NNT 20] (Appendix G Figure 3). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to trials published from 2001 to present; five trials remained, with the three trials by Fuji and colleagues and the trial by Yokote and colleagues each including two separate comparisons.^{36,38,53,135} One trial by Fuji and colleagues, one comparison from a second trial by Fuji and colleagues, and the trial by Yokote and colleagues were excluded from the analysis because no events occurred in the groups compared.^{38,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of pulmonary embolism were not significantly different [OR 0.40 (0.04 to 3.68)] (Appendix G Figure 4). A higher level of statistical heterogeneity was detected ($I^2=73.8$ percent). When limiting the original analysis to total hip replacement surgery, eight trials remained, with the trials by Fuji, Alfaro, and Yokote and colleagues each including two separate comparisons.^{35,38,42,44,49,50,52,135} The trials by Samama and Yokote and colleagues and one

comparison from the trial by Fuji and colleagues were excluded from the analysis because no events occurred in either groups compared.^{38,44,135} In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of pulmonary embolism were not significantly different [OR 0.48 (0.13 to 1.78)] (Appendix G Figure 5). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, three trials remained, with the two trials by Fuji and colleagues each including two separate comparisons.^{36,38,53} One trial by Fuji and colleagues was excluded from the analysis because no events occurred in either group compared.⁵³ In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.31 (0.03 to 3.23)] (Appendix G Figure 6). No statistical heterogeneity was detected ($I^2=0$ percent). When limiting the original analysis to hip fracture surgery, one trial by Powers and colleagues remained, with two separate comparisons.¹³² In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of pulmonary embolism was not significantly different [RR 0.30 (0.04 to 2.42)] (Appendix G Figure 7). Statistical heterogeneity could not be calculated because of too few studies.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Oral Antiplatelet Agents Versus no Prophylaxis

Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery with the trial by Alfaro and colleagues including two separate comparisons.^{35,132} In patients who received oral antiplatelet agents versus no prophylaxis the risk of pulmonary embolism was not significantly different [RR 0.35 (0.07 to 1.87)] (Appendix G Figure 8). Statistical heterogeneity was not detected ($I^2=0$ percent) and Egger's p-value could not be calculated due to the few number of studies.

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Seven randomized controlled trials and one comparison from the trial by Yokote and colleagues evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery with the two trials by Fuji and colleagues each contributing two separate comparisons.^{36,38,42,44,49,135} One trial by Samama and colleagues, the comparison from Yokote and colleagues, and one comparison from a trial by Fuji and colleagues were excluded from this analysis because no events occurred in either group compared.^{38,44,135} In patients who received injectable low molecular weight heparin versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.59 (0.17 to 2.08)] (Appendix G Figure 9). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.511).

Injectable Unfractionated Heparins Versus no Prophylaxis

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.⁵⁰ In this trial, patients who had total hip replacement surgery received either unfractionated heparin or no prophylaxis and the risk of pulmonary embolism was not significantly different [RR 0.33 (0.03 to 3.84)].

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on pulmonary embolism although the risk could not be calculated because no events occurred.¹³⁵

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.⁵³ This trial evaluated patients who had total knee replacement and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral Vitamin K Antagonists Versus no Prophylaxis

One comparison from the trial by Powers and colleagues evaluated the impact of vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery.¹³² This trial evaluated patients who had hip fracture surgery and compared warfarin with no prophylaxis. In patients who received warfarin versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)].

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.⁵¹ In this trial, a venous foot pump was compared with no prophylaxis in patients who had total knee replacement surgery. The risk of pulmonary embolism could not be calculated because no events occurred in either group compared.

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Fatal Pulmonary Embolism

Pharmacologic Prophylaxis Versus no Prophylaxis

Six trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery with the trials by Yokote, Fuji, and Powers each including two separate comparisons.^{42,44,49,53,132,135} Five trials were excluded from the analysis because no events occurred in the groups compared, leaving one comparison from the trial by Powers and colleagues.¹³² In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].

When limiting the original analysis to trials comparing pharmacologic prophylaxis to truly no prophylaxis, two trials remained with the trial by Powers and colleagues including two separate comparisons.^{49,132} One trial and one comparison from Powers and colleagues were excluded because no events occurred in the groups compared, leaving the comparison of aspirin versus no prophylaxis from Powers and colleagues. In this comparison, in patients who received

pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)]. Two trials were conducted from 2001-present, by Fuji and colleagues and Yokote and colleagues. Neither had events within the groups compared, therefore subgroup analysis was not possible.^{53,135} Subgroup analyses based on total hip replacement surgery^{42,44,49,135} and total knee replacement surgery⁵³ were not possible because the included trials had no events in either groups compared. When limiting the original analysis to hip fracture surgery one trial by Powers and colleagues remained, with two separate comparisons included.¹³² However in the comparison of warfarin to no prophylaxis no events occurred, leaving the comparison of aspirin to no prophylaxis. In this comparison, in patients receiving pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.¹⁴⁴ This study was conducted in patients who had total hip or total knee replacement surgery and included two separate comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of fatal pulmonary embolism could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significantly different in the occurrence of fatal pulmonary embolism (0.07 percent versus 0 percent, p=0.189).

Oral Antiplatelet Agents Versus no Prophylaxis

One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery. In this trial patients who had hip fracture surgery received either aspirin or no prophylaxis and the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].¹³²

One controlled observational study by Cusick and colleagues compared oral antiplatelet prophylaxis versus no prophylaxis and the results were previously described above.¹⁴⁴

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Three randomized controlled trials and one comparison from the trial by Yokote and colleagues evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{42,44,49,135} The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

Injectable Unfractionated Heparin Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparin versus no prophylaxis on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.¹³⁵ However no events occurred and the risk of fatal pulmonary embolism could not be calculated.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.⁵³ This trial evaluated patients who had total knee replacement and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral Vitamin K Antagonists Versus no Prophylaxis

One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of vitamin K antagonists versus no prophylaxis in patient who had major orthopedic surgery.¹³² This trial evaluated patients who had hip fracture surgery and received either warfarin or no prophylaxis. The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

One controlled observational study by Cusick and colleagues compared oral vitamin K antagonists versus no prophylaxis and the results were previously described above.¹⁴⁴

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.⁵¹ In this trial, a venous foot pump was compared with no prophylaxis in patients who had total knee replacement surgery. The risk of fatal pulmonary embolism could not be calculated because no events occurred in either group compared.

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Nonfatal Pulmonary Embolism

Pharmacologic Prophylaxis Versus no Prophylaxis

Six randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery with the trials by Yokote, Fuji, and Powers and colleagues each including two separate comparisons.^{42,44,49,53,132,135} Three trials were excluded from the analysis because no events occurred in either of the groups compared.^{44,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.21 (0.04 to 1.30)] (Appendix G Figure 10). Statistical heterogeneity was not detected ($I^2=0$ percent) although publication bias was detected (Egger's p-value=0.009) The directionality of the publication bias was unclear.

When limiting the analysis to trials which compared pharmacologic prophylaxis with truly no prophylaxis, two trials remained, with the trial by Powers and colleagues including two separate comparisons.^{49,132} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 0.21 (0.03 to 1.29)] (Appendix G Figure 11). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis of trials published from 2001-present was not possible because two trials remained and no events occurred in either of the groups compared.^{53,135} When limiting the original analysis to

total hip replacement, four trials remained although the trials by Yokote and Samama and colleagues were excluded because no events occurred.^{42,44,49,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.53 (0.05 to 5.09)] (Appendix G Figure 12). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis of trials evaluating total knee replacement was not possible because only one trial remained and no events occurred in either of the groups compared.⁵³ When limiting the original analysis to hip fracture surgery, one trial remained by Powers and colleagues which included two separate comparisons.¹³² In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 0.16 (0.02 to 1.53)] (Appendix G Figure 13). Statistical heterogeneity could not be evaluated because of too few studies.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.¹⁴⁴ This study was conducted in patients who had total hip or total knee replacement surgery and included two separate comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of nonfatal pulmonary embolism could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significant difference in the occurrence of nonfatal pulmonary embolism (0.67 percent versus 0 percent, $p=0.683$).

Oral Antiplatelet Agents Versus no Prophylaxis

One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery. In this trial patients who had hip fracture surgery received either aspirin or no prophylaxis and the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)].¹³² One controlled observational study by Cusik and colleagues also evaluated the impact of oral antiplatelet prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery and the results are presented above.¹⁴⁴

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Three randomized controlled trials and one comparison from the trial by Yokote and colleagues in 2011 evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{42,44,49,135} One trial and the comparison from Yokote and colleagues were excluded from the analysis because no events occurred in either group compared.^{44,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.53 (0.05 to 5.09)] (Appendix G Figure 14). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

Injectable Unfractionated Heparin Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparin versus no prophylaxis on this outcome.

Injectable or Oral Factor Xa inhibitors Versus no Prophylaxis

One comparison from the trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on nonfatal pulmonary embolism although the risk could not be calculated because no events occurred.¹³⁵

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.⁵³ This trial evaluated patients who had total knee replacement surgery and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of nonfatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral Vitamin K Antagonists Versus no Prophylaxis

One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral vitamin K antagonists versus no prophylaxis in patient who had major orthopedic surgery.¹³² This trial evaluated patients who had hip fracture surgery and received either warfarin or no prophylaxis. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)]. One controlled observational study by Cusik and colleagues also evaluated the impact of oral vitamin K antagonist prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery and the results are presented above.¹⁴⁴

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.⁵¹ In this trial, a venous foot pump was compared with no prophylaxis in patients who had total knee replacement. The risk of nonfatal pulmonary embolism could not be calculated because no events occurred in either group compared.

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Postthrombotic Syndrome

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on this outcome.

Mechanical prophylaxis versus no prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on this outcome.

Mortality

Pharmacologic Prophylaxis Versus no Prophylaxis

Ten randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery,^{40,42-45,47,49,53,132,135} of which the trials by Yokote, Fuji and Powers and colleagues each included two separate comparisons. Four trials were excluded from the analysis because no events occurred in the groups compared.^{43,44,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality were not significantly different [OR 1.23 (0.54 to 2.78)] (Appendix G Figure 15). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.757).

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared with truly no prophylaxis, five trials remained, with the trial by Powers and colleagues including two separate comparisons.^{40,43,47,49,132} The trial by McKenna and colleagues was excluded from the analysis because no events occurred in either of the groups compared. In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of mortality were not significantly different [OR 1.26 (0.52 to 3.11)] (Appendix G Figure 16). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis of trials published from 2001-present was not possible because only two trials remained and no events occurred in the groups compared.^{53,135} When limiting original pooled analysis to trials conducted in patients who had total hip replacement surgery, six trials remained.^{42,44,45,47,49,135} of which the trial by Yokote and colleagues included two separate comparisons. The trial by Yokote and Samama were excluded from the analysis because no events occurred in either of the groups compared. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality were not significantly different [OR 1.02 (0.21 to 5.10)] (Appendix G Figure 17). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting original pooled analysis to trials conducted in patients who had total knee replacement surgery, two trials remained and the risk of mortality could not be calculated because no events occurred in the groups compared.^{43,53} When limiting the original pooled analysis to hip fracture surgery, two trials remained with the trial by Powers and colleagues including two separate comparisons.^{40,132} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of mortality was not significantly different [RR 1.27 (0.50 to 3.26)] (Appendix G Figure 18). Statistical heterogeneity was not detected ($I^2=0$ percent).

Subgroup analyses based on age, gender or ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Three controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery.^{144,146,150} The first study by Cusick and colleagues evaluated patients who had either total hip or total knee replacement surgery and included two comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of mortality could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significant difference in the risk of mortality (0.32 percent versus 0 percent, p=0.902). The second study by Sachs and colleagues evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis.¹⁴⁶ No statistically significant difference in mortality was observed in this study when comparing patients who received warfarin versus no prophylaxis (0.1 percent versus 0.3 percent, p=0.863).

The third study by Gerkens and colleagues evaluated patients who had total hip or knee replacement or hip fracture surgery and included two comparisons; enoxaparin versus no prophylaxis and fondaparinux versus no prophylaxis.¹⁵⁰ There was a significant lower number of deaths in patients who received enoxaparin versus no prophylaxis (2.2 percent versus 11.2 percent, $p<0.001$) and in patients who received fondaparinux versus no prophylaxis (0.8 percent versus 11.3 percent, $p=0.002$).

Oral Antiplatelet Agents Versus no Prophylaxis

Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on mortality in patients who had major orthopedic surgery.^{43,132} The trial by McKenna and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving one comparison from the trial by Powers and colleagues. The comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of aspirin versus placebo on mortality in patients who had major orthopedic surgery. In this comparison, the odds of mortality were not significantly different in patients receiving oral antiplatelet agents versus no prophylaxis [OR 1.62 (0.39 to 6.72)].

One controlled observational study by Cusick and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis and the results have been previously described above.¹⁴⁴

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Eight randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on mortality in patients who had major orthopedic surgery.^{36,40,42,44,46,47,49,135} Three trials were excluded from the pooled analysis because no events occurred in either group.^{36,44,135} In patients who received injectable low molecular weight heparin versus no prophylaxis, the odds of mortality were not significantly different [OR 0.98 (0.32 to 3.01)] (Appendix G Figure 19). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.962).

One controlled observational study evaluated the impact of low molecular weight heparin versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparin versus no prophylaxis on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on mortality in patients who had major orthopedic surgery. No events occurred therefore the risk of mortality could not be calculated.¹³⁵

One controlled observational study evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on mortality in patients who had major orthopedic surgery.⁵³ In this trial, patients who had total knee replacement were randomized to either dabigatran 150mg daily,

dabigatran 220mg daily or placebo. The risk of mortality could not be calculated because no events occurred in the groups compared.

Oral Vitamin K Antagonists Versus no Prophylaxis

One comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of warfarin versus no prophylaxis on mortality in patients who had major orthopedic surgery.¹³² In this comparison, the odds of mortality in patients receiving warfarin compared with no prophylaxis were not significantly different [OR 1.64 (0.39 to 6.84)].

Two controlled observational studies evaluated the impact of oral vitamin K antagonists versus no prophylaxis and the results have been previously described above.^{144,146}

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on this outcome.

Mortality Due to Bleeding

Pharmacologic Prophylaxis Versus no Prophylaxis

Nine randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery with the trials by Yokote, Fuji and Powers and colleagues each included two separate comparisons.^{40,43-45,47,49,53,132,135} Eight trials were excluded from the analysis because no events occurred in the groups compared,^{40,43-45,47,53,132} leaving the trial by Turpie and colleagues which compared enoxaparin with placebo.⁴⁹ In this trial, in patients who received enoxaparin versus placebo the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)].

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared with truly no prophylaxis, five trials remained, with the trial by Powers and colleagues including two separate comparisons.^{40,43,47,49,132} Four trials were excluded from the analysis because no events occurred in the groups compared,^{40,43,47,132} leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.⁴⁹ In this trial, in patients who received enoxaparin versus placebo, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. Subgroup analysis based on trials published from 2001-present was not possible because only two trials remained and no events occurred in the groups compared.^{53,135} When limiting original pooled analysis to trials conducted in patients who had total hip replacement surgery, five trials remained.^{44,45,47,49,135} Four trials were excluded because no events occurred in the groups compared,^{44,45,47} leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.⁴⁹ In this trial, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. When limiting the original pooled analysis to trials conducted in patients who had total knee replacement surgery, two trials remained and the trial by Fuji and colleagues included two separate comparisons.^{43,53} The risk of mortality due to bleeding could not be calculated because no event occurred in the groups compared. When limiting the original pooled analysis to trials conducted in patients who had hip fracture surgery, two trials remained with the trial by Powers and colleagues contributing two separate comparisons of aspirin to placebo and warfarin to placebo.^{40,132} No events occurred in either trial group therefore the risk of mortality due to bleeding could not be calculated.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on mortality due to bleeding.¹⁵⁰ This study evaluated patients who had total hip or knee replacement or hip fracture surgery and included two comparisons; enoxaparin versus no prophylaxis and fondaparinux versus no prophylaxis.¹⁵⁰ There was no significant difference in mortality due to bleeding in patients who received enoxaparin versus no prophylaxis (0.3 percent versus 0.7 percent, $p=0.749$) and in patients who received fondaparinux versus no prophylaxis (0.0 percent versus 0.7 percent, $p=0.976$).

Oral Antiplatelet Agents Versus no Prophylaxis

One randomized controlled trial by McKenna and colleagues as well as one comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{43,132} No events occurred in either trial therefore the risk of mortality due to bleeding could not be calculated.

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Six randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{40,44,45,47,49,135} Five trials were excluded from the pooled analysis because no events occurred in either group,^{40,44,45,47,135} leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.⁴⁹ In this trial, the odds of mortality due to bleeding in patients receiving enoxaparin versus placebo were not significantly different [OR 0.14 (0.003 to 6.82)].

One controlled observational study evaluated the impact of low molecular weight heparin versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparin versus no prophylaxis on the outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on mortality due to bleeding. No events occurred in the groups compared therefore the risk of mortality due to bleeding could not be calculated.¹³⁵

One controlled observational study evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.⁵³ In this trial, patients who had total knee replacement were randomized to either dabigatran 150mg daily, dabigatran 220mg daily or placebo. The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

Oral Vitamin K Antagonists Versus no Prophylaxis

One comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of warfarin versus placebo on mortality due to bleeding in patients who had major orthopedic surgery.¹³² No events occurred in either arm therefore the risk of mortality due to bleeding could not be calculated.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on this outcome.

Health-Related Quality of Life

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on this outcome.

Deep Vein Thrombosis

Pharmacologic Prophylaxis Versus no Prophylaxis

Seventeen randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery, with the three trial by trials by Yokote, Fuji, Alfaro and colleagues each including two separate comparisons.^{35,36,38,40-45,47,49,50,52,53,133,135} In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.56 (0.47 to 0.68), NNT 3 to 33] (Appendix G Figure 20). A higher level of statistical heterogeneity was detected but publication bias was not detected ($I^2=52.8$ percent, Egger's p-value=0.199). Higher statistical heterogeneity may reflect the different pharmacologic agents evaluated across trials, the inclusion of all major orthopedic surgeries, and the changes in clinical practice over the years which trials were conducted.

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared with truly no prophylaxis, nine trials remained, with the trial by Alfaro and colleagues including two separate comparisons.^{35,36,40,41,43,47,49,50,133} In patients who received pharmacologic prophylaxis versus truly no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.44 (0.27 to 0.72), NNT 2 to 9] (Appendix G Figure 21). A higher level of statistical heterogeneity was detected ($I^2=69$ percent). When limiting the original pooled analysis to trials published from 2001-present, five trials remained, with the trials by Yokote and by Fuji and colleagues each including two separate comparisons.^{36,38,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.54 (0.45 to 0.64), NNT 4 to 31] (Appendix G Figure 22). A lower level of statistical heterogeneity was detected ($I^2=10.4$ percent). When limiting the original pooled analysis to total hip replacement surgery, twelve trials remained,^{35,38,41,42,44,45,47,49,50,52,133,135} of which the trials by Yokote, Fuji and Alfaro and colleagues each included two separate comparisons. In patients who received pharmacologic

prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.59 (0.45 to 0.77), NNT 3 to 35] (Appendix G Figure 23). A higher level of statistical heterogeneity was detected ($I^2=52.9$ percent). When limiting original pooled analysis to total knee replacement, four trials remained,^{36,38,43,53} of which the two trials by Fuji and colleagues each included two separate comparisons. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.54 (0.40 to 0.73), NNT 3 to 10] (Appendix G Figure 24). A higher level of statistical heterogeneity was detected ($I^2=61.4$ percent). When limiting the original pooled analysis to hip fracture surgery, one trial remained.⁴⁰ In this trial, the risk of developing deep vein thrombosis in patients who received pharmacologic prophylaxis versus no prophylaxis was significantly decreased [RR 0.35 (0.15 to 0.78), NNT 4].

Two randomized controlled trial evaluated the impact of age on the incidence of deep vein thrombosis in patients who had major orthopedic surgery.^{41,43} The first trial by Kim and colleagues randomized patients to aspirin or no prophylaxis and performed subgroup analysis on the incidence of deep vein thrombosis based on patients with an age below 60 years versus age above 60 years. The incidence of deep vein thrombosis was not significantly different in the patients who received aspirin versus no prophylaxis in the subgroup aged below 60 years ($p=0.426$) or in the subgroup aged above 60 years ($p=0.232$).⁴¹ The second trial by McKenna and colleagues randomized patients to aspirin or no prophylaxis. When adjusting for age, the odds of deep vein thrombosis were not significantly different in patients who received aspirin versus no prophylaxis [AOR 1.30 (-2.16 to 4.76)].⁴³

The trial by Kim and colleagues also evaluated the impact of gender on the incidence of deep vein thrombosis in patients who received aspirin versus no prophylaxis.⁴¹ There were no significant differences in the incidence of deep vein thrombosis in male patients ($p=0.322$) or in female patients ($p=0.117$) who received aspirin prophylaxis versus no prophylaxis. A second trial by Alfaro and colleagues found a significantly lower incidence of deep vein thrombosis in male patients who received aspirin prophylaxis versus no prophylaxis (0 percent versus 26 percent, $p<0.04$).

Subgroup analysis based on ethnicity was not possible because no randomized controlled trials reported data based on these subgroups.

Oral Antiplatelet Agents Versus no Prophylaxis

Three randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery,^{35,41,43} of which the trial by Alfaro and colleagues included two separate comparisons; aspirin 250mg per day versus no prophylaxis and aspirin 1 gram per day versus no prophylaxis. In patients who received oral antiplatelet agents versus no prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.41 (0.12 to 1.32)] (Appendix G Figure 25). A higher level of statistical heterogeneity was detected as was the presence of publication bias although the directionality of the publication bias was unclear ($I^2=76$ percent, Egger's p -value=0.002).

Injectable Low Molecular Weight Heparins Versus no Prophylaxis

Twelve randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{36,38,40,42,44,45,47,49,52,133,135} The two trials by Fuji and colleagues included 2 separate comparisons of pharmacologic prophylaxis versus no prophylaxis. In patients who received low molecular weight heparin versus no prophylaxis, the risk of deep vein thrombosis was

significantly decreased [RR 0.54 (0.44 to 0.67), NNT 4 to 31] (Appendix G Figure 26). A higher level of statistical heterogeneity was detected although publication bias was not detected ($I^2=50.2$ percent, Egger's p -value=0.088).

Injectable Unfractionated Heparins Versus no Prophylaxis

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.⁵⁰ In this trial, the risk of deep vein thrombosis in patients receiving injectable unfractionated heparin compared with no prophylaxis was not significantly different [RR 1.60 (0.66 to 4.05)].

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.¹³⁵ In this trial patients who had total hip replacement surgery received either fondaparinux 2.5 mg daily or placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received fondaparinux versus no prophylaxis the risk of deep vein thrombosis was not significantly different [RR 0.99 (0.35 to 2.80)]. Statistical heterogeneity and publication bias could not be calculated because of there was only one trial available.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.⁵³ In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.51 (0.37 to 0.69), NNT 4] (Appendix G Figure 27). Statistical heterogeneity and publication bias could not be calculated because of too few studies. Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral vitamin K antagonists versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.³⁷ In this trial, patients who had total hip replacement received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also wore graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.26 (0.10 to 0.65), NNT 4].

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent

pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery.

Asymptomatic Deep Vein Thrombosis

Pharmacologic Prophylaxis Versus no Prophylaxis

Three randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery and the trial by Fuji and colleagues included two separate comparisons.^{42,44,53} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.52 (0.40 to 0.69), NNT 4 to 6] (Appendix G Figure 28). A lower level of statistical heterogeneity was detected although publication bias was not detected ($I^2=32.7$ percent, Egger's p-value=0.168).

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible because all three trials allowed concurrent use of graduated compression stockings along with the intervention patients were randomized to.^{42,44,53} When limiting the original analysis to trials published from 2001-present, one trial remained by Fuji and colleagues which included two separate comparisons; dabigatran 150mg daily or dabigatran 220mg daily versus no prophylaxis.⁵³ In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.37 to 0.67), NNT 4] (Appendix G Figure 29). Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat. Statistical heterogeneity could not be calculated because there were too few studies. This is also the same result that is obtained when limiting the original analysis to total knee replacement surgery since the trial by Fuji and colleagues was the only trial which fit this subgroup.⁵³ When limiting the original analysis to total hip replacement, two trials remained.^{42,44} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.52 (0.27 to 1.00)] (Appendix G Figure 30). Statistical heterogeneity could not be calculated because there were too few studies. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

Subgroup analysis based on age, gender or ethnicity was not possible because no randomized controlled trials reported data based on these subgroups.

Oral Antiplatelet Agents Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Two trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{42,44} Both of these trials were conducted in patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparins versus no prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.52 (0.27 to 1.00)] (Appendix G Figure 30). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on this outcome.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁵³ In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.37 to 0.67), NNT 4] (Appendix G Figure 29). Statistical heterogeneity and publication bias could not be calculated because of too few studies. Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.

Symptomatic Deep Vein Thrombosis

Pharmacologic Prophylaxis Versus no Prophylaxis

Four randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery and the trial by Yokote, Fuji and colleagues included two separate comparisons.^{42,44,53} One trial and one comparison from the trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the groups compared.^{42,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.07 (0.25 to 4.52)] (Appendix G Figure 31). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.316).

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible because all three trials allowed concurrent use of graduated compression stockings along with the intervention patients were randomized to.^{42,44,53} When limiting the original analysis to trials published from 2001- present, two trials by Yokote and Fuji and colleagues remained, both of which included two separate comparisons..^{53,135} One of the two comparisons by Yokote and colleagues was excluded because no events occurred in either of

the arms. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.11 (0.20 to 6.01)] (Appendix G Figure 32). No statistical heterogeneity was detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement, three trials remained with the trial by Yokote and colleagues including two separate comparisons.^{42,44,135} One of the two comparisons and the trial by Lassen and colleagues were excluded from the analysis because no events occurred in the groups compared, leaving one comparison from the trial by Yokote and the trial by Samama and colleagues.^{42,44,135} (Appendix G Figure 33) In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.90 (0.20 to 18.32)]. Statistical heterogeneity could not be calculated because there were too few studies. When limiting the original analysis to total knee replacement surgery, two comparisons from the trial by Fuji and colleagues remained. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.72 (0.12 to 4.39)] (Appendix G Figure 34). Statistical heterogeneity could not be calculated because only one trial was available. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

Subgroup analysis based on age, gender or ethnicity was not possible because no randomized controlled trials reported data based on these subgroups.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.¹⁴⁶ This trial evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. No statistically significant difference in symptomatic deep vein thrombosis was observed in this study when comparing patients who received warfarin versus no prophylaxis (0.2 percent versus 0 percent, $p=0.568$).

Oral Antiplatelet Agents Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable low Molecular Weight Heparins Versus no Prophylaxis

Three trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{42,44,135} All of these trials were conducted in patients who had total hip replacement surgery. The trial by Yokote and Lassen and colleagues were excluded from the analysis because no events occurred in the groups compared, leaving the trial by Samama and colleagues. In this trial, in patients who received injectable low molecular weight heparins versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.96 (0.06 to 15.52)]. Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on symptomatic deep vein thrombosis.¹³⁵ In this trial, patients were randomized to receive either fondaparinux 2.5mg daily or placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received injectable or oral factor Xa inhibitors versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 7.30 (0.14 to 368.00)]. Statistical heterogeneity and publication bias could not be calculated because of too few studies.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁵³ In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.72 (0.12 to 4.39)] (Appendix G Figure 34). Statistical heterogeneity and publication bias could not be calculated because of too few studies.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral vitamin K antagonists versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.

Proximal Deep Vein Thrombosis

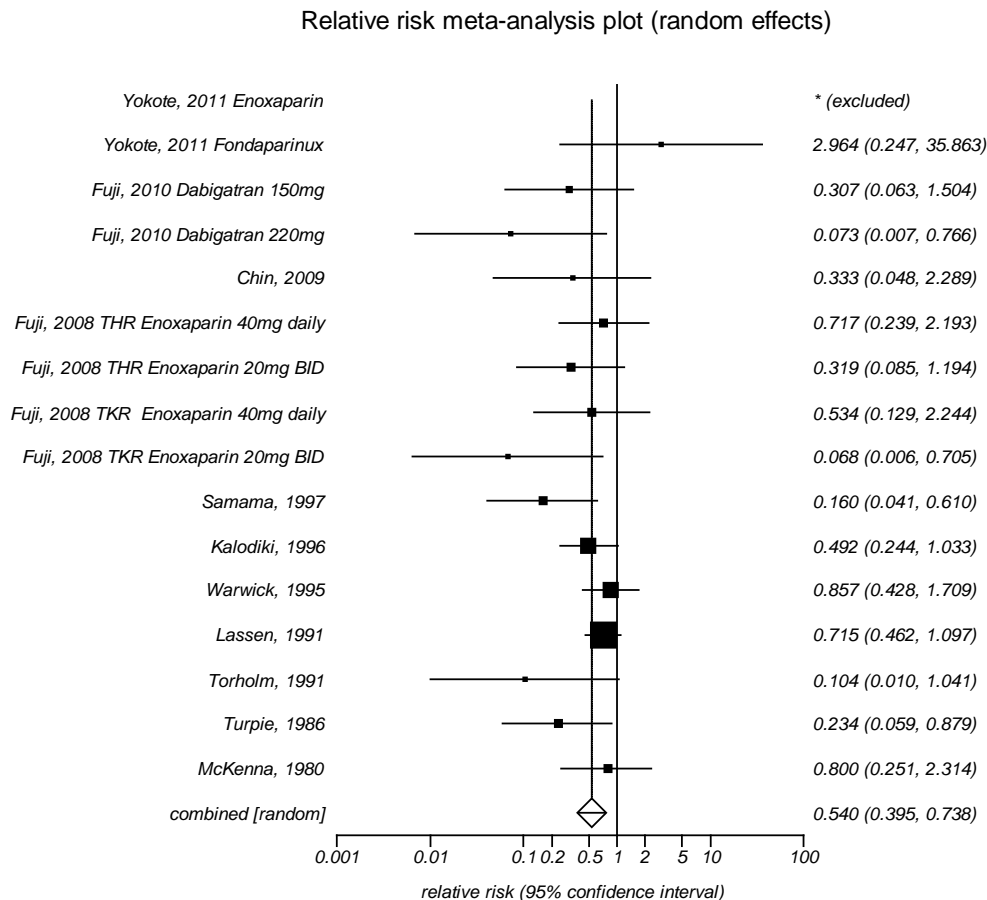
Pharmacologic Prophylaxis Versus no Prophylaxis

Twelve randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery with one trial by Yokote and three trials by Fuji and colleagues each including two separate comparisons.^{36,38,42-44,47,49,52,53,133,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.53 (0.39 to 0.74), NNT 4 to 213] (Figure 4). A lower level of statistical heterogeneity was detected as was the presence of publication bias for studies in which the risk of proximal deep vein thrombosis was increased ($I^2=9.7$ percent, Egger's p-value 0.012).

When limiting the original analysis to trials which compared pharmacologic prophylaxis to truly no prophylaxis, five trials remained.^{36,43,47,49,133} In patients who received pharmacologic prophylaxis versus truly no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.46 (0.27 to 0.79), NNT 4 to 68] (Appendix G Figure 35). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to trials published from 2001-present, five trials remained; one trial by Yokote and the three trials

by Fuji and colleagues each included two separate comparisons.^{36,38,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.42 (0.22 to 0.79), NNT 18 to 173] (Appendix G Figure 36). Statistical heterogeneity was not detected ($I^2=0$ percent).

Figure 4. Impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 9.7 percent

Egger's p-value: 0.012

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

When limiting the original analysis to total hip replacement surgery, eight trials remained with the trial by Yokote and the trial by Fuji and colleagues including two separate comparisons.^{38,42,44,47,49,52,133,135} One comparison from the trial by Yokote and colleagues was excluded because no events occurred in the groups compared. In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.56 (0.38 to 0.81), NNT 4] (Appendix G Figure 37). A range for the NNT could not be calculated because the lower limit of the control event rate was zero. A lower level of statistical heterogeneity was detected ($I^2=20.9$ percent). When limiting the original analysis to total knee replacement surgery four trials remained and the two trials by Fuji and colleagues each included two separate comparisons.^{36,38,43,53} In patients who received

pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.43 (0.21 to 0.88), NNT 5 to 65] (Appendix G Figure 38). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

Subgroup analysis based on age, gender or ethnicity was not possible because none of the randomized controlled trials reported data based on these subgroups.

Oral Antiplatelet Agents Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral antiplatelet agents versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.⁴³ In this trial, patients who had total knee replacement were randomized to either aspirin or no prophylaxis. In patients who received oral antiplatelet agents versus no prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.80 (0.25 to 2.31)].

Injectable Low Molecular Weight Heparins Versus no Prophylaxis

Nine trials plus one comparison from trial by Yokote and colleagues evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{36,38,42,44,47,49,52,133,135} The two trials by Fuji and colleagues each included two separate comparisons and the comparison by Yokote and colleagues was excluded from the analysis because no events occurred in the groups compared. In patients who received injectable low molecular weight heparins versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.53 (0.38 to 0.75), NNT 4] (Appendix G Figure 39). A range for the NNT could not be calculated because the lower limit of the control event rate was zero. A lower level of statistical heterogeneity was detected as was the presence of publication bias ($I^2=14.3$ percent, Egger's p -value=0.003). The directionality of the publication bias was unclear.

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on proximal deep vein thrombosis.¹³⁵ In this trial, patients who had total hip replacement surgery were randomized to fondaparinux 2.5mg daily or placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received injectable or oral factor Xa inhibitors versus no prophylaxis the odds of proximal deep vein thrombosis were not significantly different [OR 7.30 (0.14 to 368.00)]. Statistical heterogeneity and publication bias could not be evaluated because there was only one trial available.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.⁵³ In this trial patients who had total knee replacement were randomized to dabigatran

150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.21 (0.05 to 0.95), NNT 21] (Appendix G Figure 40). Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat. Statistical heterogeneity could not be evaluated because of too few studies.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral vitamin K antagonists versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.³⁷ In this trial, patients who had total hip replacement surgery received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also received graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.41 (0.10 to 1.72)].

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery.

Distal Deep Vein Thrombosis

Pharmacologic Prophylaxis Versus no Prophylaxis

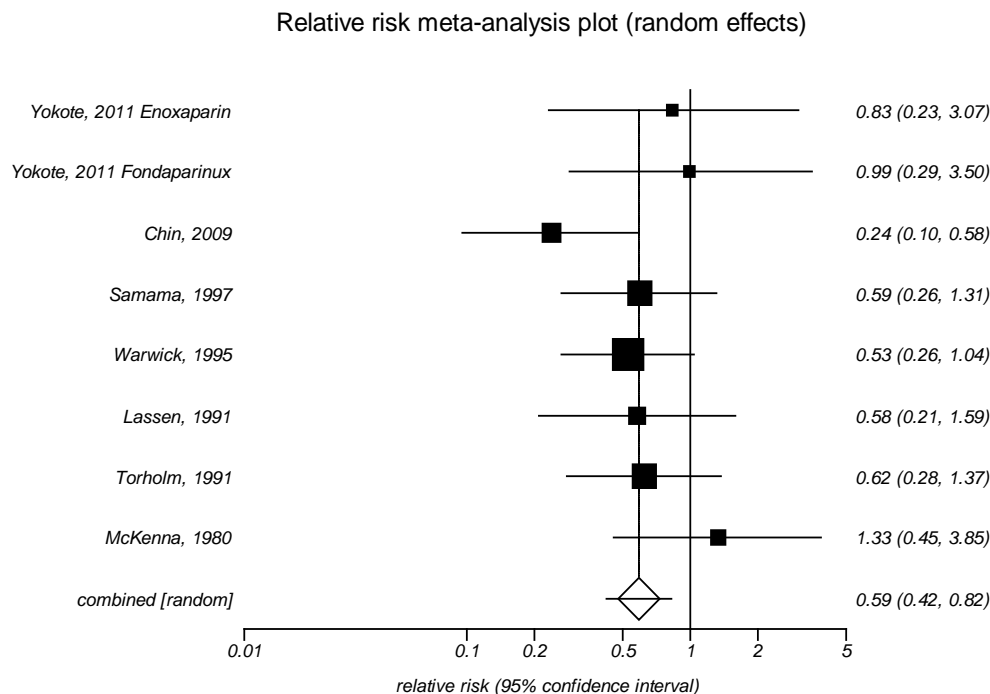
Seven randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery with the trial by Yokote and colleagues including two separate comparisons.^{36,42-44,47,52,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.59 (0.42 to 0.82), NNT 8 to 35] (Figure 5). Statistical heterogeneity and publication bias were not detected. ($I^2=0$ percent, Egger's p-value=0.305).

When limiting the original analysis to trials in which pharmacologic prophylaxis was compared with truly no prophylaxis, three trials remained.^{36,43,47} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.57 (0.22 to 1.46) (Appendix G Figure 41). A higher level of statistical heterogeneity was detected ($I^2=66.8$ percent). When limiting the original analysis to trials published from 2001-present, two trials remained with the trial by Yokote and colleagues including two separate comparisons.^{36,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.52 (0.20 to 1.38),] (Appendix G Figure 42). A lower level of statistical heterogeneity was detected ($I^2=48.9$ percent). When limiting the original analysis to total hip replacement surgery, five trials remained with the trial by Yokote and colleagues including two separate comparisons.^{42,44,47,52,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.62 (0.42 to

0.90), NNT 12 to 38] (Appendix G Figure 43). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained.^{36,43} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.55 (0.10 to 3.19)] (Appendix G Figure 44). Statistical heterogeneity could not be calculated because of too few studies. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

Subgroup analysis based on age, gender or ethnicity was not possible because none of the randomized controlled trials reported data based on these subgroups.

Figure 5. Impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 0 percent

Egger's p-value: 0.305

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Oral Antiplatelet Agents Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral antiplatelet agents versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.⁴³ In this trial, patients who had total knee replacement were randomized to either aspirin or no prophylaxis. In patients who received oral antiplatelet agents versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 1.33 (0.45 to 3.84)].

Injectable Low Molecular Weight Heparins Versus no Prophylaxis

Six trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.^{36,42,44,47,52,135} In

patients who received injectable low molecular weight heparins versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.52 (0.37 to 0.75), NNT 9 to 30] (Appendix G Figure 45). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.892).

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis in patients who had major orthopedic surgery on distal deep vein thrombosis. In this trial, patients who had total hip replacement received either fondaparinux 2.5mg daily or placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received injectable or oral factor Xa inhibitors versus no prophylaxis, the risk of distal deep vein thrombosis were not significantly different [RR 0.99 (0.35 to 2.80)]. Statistical heterogeneity could not be evaluated because there was only one trial available.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable or oral direct thrombin inhibitors versus no prophylaxis in patients who had major orthopedic on this outcome.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral vitamin K antagonists versus no prophylaxis in patients who had major orthopedic on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.³⁷ In this trial, patients who had total hip replacement surgery received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also received graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of distal deep vein thrombosis was not significantly different [RR 0.68 (0.14 to 3.26)].

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of either graduated compression stockings or intermittent pneumatic compression devices versus no prophylaxis in patients who had major orthopedic surgery.

Major Bleeding

Pharmacologic Prophylaxis Versus no Prophylaxis

Eight randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery.^{38,41,44,49,53,132,135} One trial by Yokote, one trial by Powers and three trials by Fuji and colleagues each included two separate comparisons.^{38,53,132,135} The trials by Yokote and Kim were excluded from the

analysis because no events occurred in either group.^{41,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.74 (0.36 to 1.51)] (Appendix G Figure 46). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.707).

When limiting to trials that compared pharmacologic prophylaxis to truly no prophylaxis, four trials remained.^{41,49,132} The trial by Powers and colleagues included two separate comparisons.¹³² The trial by Kim and colleagues was excluded from the analysis because no events occurred in either group.⁴¹ In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of major bleeding were not significantly different [OR 0.53 (0.17 to 1.64)] (Appendix G Figure 47). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to trials published from 2001-present; four trials remained with the trial by Yokote and three trials by Fuji and colleagues including two separate comparisons.^{38,53,135} The trial by Yokote was excluded from the analysis because no events occurred in the groups compared. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR 0.87 (0.31 to 2.45)] (Appendix G Figure 48). Statistical heterogeneity was not detected ($I^2=0$ percent).

When limiting the original analysis to total hip replacement surgery, five trials remained, with the trials by Yokote and by Fuji and colleagues providing two separate comparisons.^{38,41,44,49,135} The trials by Yokote and Kim and colleagues were excluded from the analysis because no events occurred in either group. In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of major bleeding were not significantly different [OR 1.61 (0.44 to 5.83)] (Appendix G Figure 49). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained by Fuji and colleagues and both trials provided two separate comparisons.^{38,53} In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR 0.59 (0.18 to 1.95)] (Appendix G Figure 50). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to hip fracture surgery, one trial by Powers and colleagues remained and provided two separate comparisons.¹³² In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding were not significantly different [RR 0.55 (0.12 to 2.51)] (Appendix G Figure 51). Statistical heterogeneity was not detected ($I^2=0$ percent).

Subgroup analysis based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding.¹⁵⁰ This study evaluated patients who had total hip or knee replacement or hip fracture surgery and included two comparisons; enoxaparin versus no prophylaxis and fondaparinux versus no prophylaxis.¹⁵⁰ There was no significant difference in major bleeding in patients who received enoxaparin versus no prophylaxis (1.1 percent versus 0.9 percent, p=0.793) and in patients who received fondaparinux versus no prophylaxis (0.0 percent versus 0.9 percent, p=0.976).

Oral Antiplatelet Agents Versus no Prophylaxis

Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on major bleeding in patients undergoing major orthopedic surgery.^{41,132} The trial by Kim and colleagues was excluded from the analysis because no events occurred in either group, leaving the trial by Powers and colleagues. In this trial, in patients who received pharmacologic

prophylaxis versus no prophylaxis, the odds of major bleeding were not significantly different [OR 0.24 (0.05 to 1.22)].

Injectable Low Molecular Weight Heparins Versus no Prophylaxis

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on major bleeding in patients who had major orthopedic surgery with the trials by Fuji and colleagues including two separate comparisons.^{38,44,49,53,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either group. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR 0.78 (0.29 to 2.08)] (Appendix G Figure 52). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.275).

One controlled observational study evaluated the impact of injectable low molecular weight heparin versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis in patients who had major orthopedic surgery on major bleeding. However the risk of major bleeding could not be calculated because no events occurred in the groups compared.¹³⁵

One controlled observational study evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis and the results have been previously described above.¹⁵⁰

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on major bleeding in patients who had major orthopedic surgery and included two separate comparisons.⁵³ In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.96 (0.09 to 10.73)] (Appendix G Figure 53). Statistical heterogeneity and publication bias could not be calculated because of too few studies.

Oral Vitamin K Antagonists Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonists versus no prophylaxis on major bleeding in patients undergoing major orthopedic surgery.¹³² In patients who received oral vitamin K antagonist prophylaxis versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.97 (0.29 to 3.19)].

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Major Bleeding Leading to Reoperation

Pharmacologic Prophylaxis Versus no Prophylaxis

Two randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery on this outcome and the trial by Fuji and colleagues included two separate comparisons.^{44,53} The trial by Samama and colleagues and the comparison of dabigatran 150mg versus placebo from the trial by Fuji and colleagues were excluded from the analysis because no events occurred in the groups compared. The comparison of dabigatran 220mg versus placebo from the trial by Fuji and colleagues which evaluated patients who had total knee replacement surgery remained. In this trial, patients were also allowed to receive elastic compression stockings. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.11 (0.14 to 358.50)].

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible since both trials allowed the use of elastic stockings.^{44,53} When limiting the original analysis to trials published from 2001- present one trial remained and included two separate comparisons.⁵³ One comparison was excluded from the analysis because no events occurred leaving the second comparison of dabigatran 220mg versus no prophylaxis. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.11 (0.14 to 358.50)]. This is also the same result that is obtained when limiting the original analysis to total knee replacement surgery. Subgroup analysis based on total hip replacement was not possible because one trial remained and no events occurred in the groups compared.⁴⁴ Subgroup analysis limited to hip fracture surgery was not possible because none of the studies were conducted in this surgical population.

Subgroup analysis based on age, gender or ethnicity was not possible because none of the randomized controlled trials reported data based on these subgroups.

Oral Antiplatelet Agents Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable low Molecular Weight Heparins Versus no Prophylaxis

One randomized controlled trial evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.⁴⁴ However the risk of major bleeding leading to reoperation could not be calculated because no events occurred in the groups compared.

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis on this outcome.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery and included two separate comparisons.⁵³ One comparison was excluded from the analysis because no events occurred leaving the second comparison of dabigatran 220mg versus no prophylaxis. In this comparison, in patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of major bleeding leading to reoperation was not significantly different [OR 7.11 (0.14 to 358.50)].

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonists versus no prophylaxis on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Minor Bleeding

Pharmacologic Prophylaxis Versus no Prophylaxis

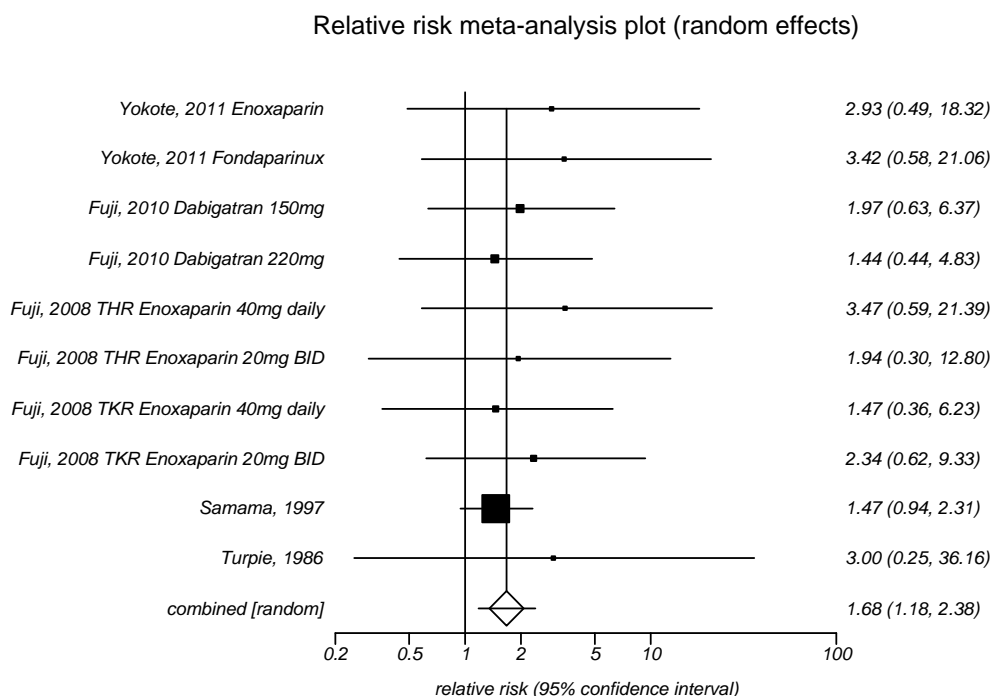
Six randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery, with one trial by Yokote and three trials by Fuji and colleagues each contributing two separate comparisons.^{38,44,49,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.67 (1.18 to 2.38), NNH 30 to 75] (Figure 6). Statistical heterogeneity was not detected, but publication was detected for studies in which the risk of bleeding was decreased ($I^2=0$ percent, Egger's p -value=0.005).

When limiting the original analysis to trials that compared pharmacologic prophylaxis to truly no prophylaxis, one trial remained.⁴⁹ In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of minor bleeding were not significantly different [OR 7.39 (0.15 to 372.38)]. When limiting the original analysis to trials published from 2001-present; one trial by Yokote and three trials by Fuji and colleagues remained and all four trials provided two separate comparisons.^{38,53,135} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 2.04 (1.16 to 3.62), NNH 20 to 49] (Appendix G Figure 54). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to trials that compared pharmacologic prophylaxis to no prophylaxis in patients undergoing total hip replacement surgery, four trials remained, with the trial by Fuji and colleagues providing two separate comparisons.^{38,44,49} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.65 (1.09 to 2.48), NNH 6 to 154] (Appendix G Figure 55). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to trials that compared pharmacologic prophylaxis to no prophylaxis in patients undergoing total knee replacement surgery, two trials remained, with both the trials by Fuji and colleagues providing two separate comparisons.^{38,53} In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was not significantly different [RR 1.77 (0.89 to 3.49)] (Appendix G Figure 56). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup

analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analysis based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Figure 6. Impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery



I^2 : 0 percent

Egger's p-value: 0.005

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Oral Antiplatelet Agents Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparins Versus no Prophylaxis

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{38,44,49,135} The two trials by Fuji and colleagues provided two separate comparisons. In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.66 (1.13 to 2.44) NNH 6 to 152] (Appendix G Figure 57). Statistical heterogeneity was not detected, but publication bias was detected for studies in which the risk of minor bleeding was decreased (I^2 =0 percent, Egger's p-value=0.029).

Injectable Unfractionated Heparins Versus no Prophylaxis

No randomized controlled trials evaluated the impact of injectable unfractionated heparins versus no prophylaxis in patients undergoing major orthopedic surgery on this outcome.

Injectable or Oral Factor Xa Inhibitors Versus no Prophylaxis

One comparison from the randomized controlled trial by Yokote and colleagues in 2011 evaluated the impact of injectable or oral factor Xa inhibitors versus no prophylaxis in patients who had major orthopedic surgery on minor bleeding. In this trial, patients who had total hip replacement surgery received either fondaparinux 2.5mg daily or placebo. The use of concurrent elastic stockings and compression devices was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received injectable or oral factor Xa inhibitors versus no prophylaxis, the odds of minor bleeding were not significantly different [OR 3.21 (0.84 to 12.24)]. Statistical heterogeneity and publication bias could not be evaluated because only one trial was available.

Injectable or Oral Direct Thrombin Inhibitors Versus no Prophylaxis

One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery and included two separate comparisons.⁵³ In patients who received oral direct thrombin inhibitors versus no prophylaxis the odds of minor bleeding were not significantly different [OR 1.67 (0.73 to 3.84)] (Appendix G Figure 58). Statistical heterogeneity and publication bias could not be calculated because of too few studies.

Oral Vitamin K Antagonists Versus no Prophylaxis

No randomized controlled trials evaluated the impact of oral vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Surgical Site Bleeding

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Infection

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Transfusion

Pharmacologic Prophylaxis Versus no Prophylaxis

One randomized controlled trial evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery and included two comparisons.⁵³ This trial evaluated patients who had total knee replacement and randomized patients to one of three groups; dabigatran 150mg daily, dabigatran 220mg daily or placebo. Patients were also allowed to receive elastic compression stockings. The comparison of dabigatran 150mg versus no prophylaxis was excluded from the analysis because no events occurred in the groups compared, leaving the dabigatran 220mg versus no prophylaxis comparison. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of bleeding leading to transfusion were not significantly different [OR 7.11 (0.14 to 358.50)]. Statistical heterogeneity and publication bias could not be calculated because of too few studies.

Subgroup analyses were not possible because only one trial was available. No randomized controlled trials evaluated the impact of prophylaxis with oral antiplatelet agents, injectable low molecular weight heparins, unfractionated heparin, injectable or oral factor Xa inhibitors, or vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.¹⁴⁶ This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. In patients who received warfarin versus no prophylaxis the risk of bleeding leading to transfusion was not significantly different (0.1 percent versus 0 percent, $p=0.921$).

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Heparin-Induced Thrombocytopenia

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Discomfort

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Readmission

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on readmission in patients who had major orthopedic surgery.¹⁴⁶ This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. No statistically significant difference in readmission rate was observed when comparing patients who received warfarin to those who received control (1.8 percent versus 0.9 percent, $p=0.171$). The reasons reported for readmission in the control group included nonfatal pulmonary embolism, superficial wound infection, and deep wound infection and those reported for the warfarin group included superficial wound infection, deep wound infection, swelling without signs of infection, myocardial infarction, and angina.

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Reoperation

Pharmacologic Prophylaxis Versus no Prophylaxis

No randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on reoperation in patients who had major orthopedic surgery.¹⁴⁶ This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. Patients who received warfarin prophylaxis had a significantly higher rate of reoperation compared with patients who received no prophylaxis (1.1 percent versus 0.3 percent, $p < 0.01$).

Mechanical Prophylaxis Versus no Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of mechanical prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Strength of Evidence and Applicability of the Body of Evidence

When comparing pharmacologic prophylaxis to no prophylaxis in Key Question 4, there was high strength of evidence that pharmacologic prophylaxis decreased the risk of proximal or of distal deep vein thrombosis and that there was a significant increase in the risk of minor bleeding. There was moderate strength of evidence that the risk of deep vein thrombosis and asymptomatic deep vein thrombosis were decreased, and that the risk of symptomatic deep vein thrombosis, mortality, or major bleeding were no different. Strength of evidence was low that there was no difference in the risk of pulmonary embolism or nonfatal pulmonary embolism and that there was a decrease in the risk of major venous thromboembolism and insufficient for all other outcomes. When comparing mechanical prophylaxis to no prophylaxis, all outcomes were rated as insufficient due to the paucity of data for this comparison.

For Key Question 4 the overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data.

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery*

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Symptomatic objectively confirmed VTE	Pharmacologic versus no prophylaxis	1 RCT (2 comp)	No	No events in the groups compared in one comparison; the remaining comparison showed OR: 7.30 (0.14 to 368.00)	NA
	• 2001-present	1 RCT (2 comp)	No	No events in the groups compared in one comparison; the remaining comparison showed OR: 7.30 (0.14 to 368.00)	NA
	• THR	1 RCT (2 comp)	No	No events in the groups compared in one comparison; the remaining comparison showed OR: 7.30 (0.14 to 368.00)	NA
	Injectable low molecular weight heparin versus no prophylaxis	1 RCT (1 comp)	No	No events in the groups compared	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	OR: 7.30 (0.14 to 368.00)	NA
	Mechanical versus no prophylaxis	0	---	---	---
Major VTE	Pharmacologic versus no prophylaxis	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)†	NA
	• 2001-present	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)†	NA
	• TKR	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)†	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)†	NA
	Mechanical versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
PE	Pharmacologic versus no prophylaxis	12 RCTs	Yes	3 trials had no events; the remaining trials showed OR 0.38 (0.13 to 1.07)	0
	• Comparing to truly no prophylaxis	5 RCTs	Yes	RR 0.30 (0.09 to 0.99) [†]	0
	• 2001-present	5 RCTs	Yes	2 trials and one comparison from one trial had no events; the remaining trials showed OR 0.40 (0.04 to 3.68)	73.8
	• THR	8 RCTs	Yes	2 trials and one comparison from one trial had no events; the remaining trials showed OR 0.48 (0.13 to 1.78)	0
	• TKR	3 RCTs	Yes	1 trial had no events; the remaining trials showed OR 0.31 (0.03 to 3.23)	0
	• HFS	1 RCT (2 comp)	Yes	RR 0.30 (0.04 to 2.42)	NA
	Oral antiplatelet agents versus no prophylaxis	2 RCTs	Yes	RR 0.35 (0.07 to 1.87)	0
	Injectable low molecular weight heparin versus no prophylaxis	7 RCTs + 1 comp	Yes	1 trial and 2 comparisons from 2 trials had no events; the remaining trials showed OR 0.59 (0.17 to 2.08)	0
	Injectable unfractionated heparin versus no prophylaxis	1 RCT	No	RR 0.33 (0.03 to 3.84)	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	No events in the groups compared	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	No events in groups compared	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
	Mechanical versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Fatal PE	Pharmacologic versus no prophylaxis	6 RCTs 1 OBS	No	Five trials and 1 comparison from one trial had no events; the remaining comparison showed OR 7.06 (0.14 to 356.21). The observational study was inconclusive.	NA
	• Comparing to truly no prophylaxis	2 RCTs	No	One trial and one comparison of one trial had no events; the remaining comparison showed OR 7.06 (0.14 to 356.21).	NA
	• 2001-present	2 RCT 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
	• THR	4 RCTs 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
	• TKR	1 RCT 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
	• HFS	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.06 (0.14 to 356.21).	NA
	Oral antiplatelet agents versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	OR 7.06 (0.14 to 356.21). The observational study was inconclusive.	NA
	Injectable low molecular weight heparin versus no prophylaxis	3 RCTs + 1 comp	No	No events in the groups compared	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	No events in the groups compared	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	No events in the groups compared	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
	Mechanical prophylaxis versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Nonfatal PE	Pharmacologic versus no prophylaxis	6 RCTs 1 OBS	Yes (RCT)	Three trials had no event; the remaining trials showed OR 0.21 (0.04 to 1.30); Observational data suggest no significant difference	0
	• Comparing to truly no prophylaxis	2 RCTs	Yes	RR 0.21 (0.03 to 1.29)	0
	• 2001-present	2 RCT	No	No events in the groups compared	NA
	• THR	4 RCTs	Yes	Two trials had no events ; the remaining trials showed OR 0.53 (0.05 to 5.09)	NA
	• TKR	1 RCT	No	No events in the groups compared	NA
	• HFS	1 RCT (2 comp)	Yes	RR 0.16 (0.02 to 1.53)	NA
	Oral antiplatelet agents versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
	Injectable low molecular weight heparin versus no prophylaxis	3 RCTs + 1 comp	Yes	One trial and 1 comparison from one trial had no events; the remaining trials showed OR 0.53 (0.05 to 5.09)	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	No events in the groups compared	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
	Mechanical prophylaxis versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
PTS	Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Mortality	Pharmacologic versus no prophylaxis	10 RCTs 3 OBS	Yes (RCTs)	Four trials had no events; the remaining trials showed OR: 1.23 (0.54 to 2.78). Two observational studies suggested no difference while 1 study suggested decrease number of deaths with prophylaxis.	0
	• Comparing to truly no prophylaxis	5 RCTs	Yes	1 trial had no events; the remaining trials showed OR: 1.26 (0.52 to 3.11)	0
	• 2001-present	2 RCT 3 OBS	No	No events in the groups compared. Two observational studies suggested no difference while 1 study suggested decrease number of deaths with prophylaxis.	NA
	• THR	6 RCTs 1 OBS	Yes	Two trials had no events; the remaining showed OR: 1.02 (0.21 to 5.10). Observational study was inconclusive.	0
	• TKR	2 RCTs 2 OBS	No	No events in either arm. Observational studies showed no difference.	NA
	• HFS	2 RCTs	Yes	RR: 1.27 (0.50 to 3.26)	0
	Oral antiplatelet agents versus no prophylaxis	2 RCTs 1 OBS	No	One trial had no events; the remaining trial showed OR: 1.62 (0.39 to 6.72). The observational study was inconclusive.	0
	Injectable low molecular weight heparin versus no prophylaxis	8 RCTs 1 OBS	Yes (RCT)	Three trials showed no events; the remaining showed OR: 0.98 (0.32 to 3.01); observational data suggested decreased deaths with prophylaxis	0
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	No events in the groups compared; observational data suggested decreased deaths with prophylaxis	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	OR: 1.64 (0.39 to 6.84). The observational study showed no difference.	NA
	Mechanical versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Mortality due to bleeding	Pharmacologic versus no prophylaxis	9 RCTs 1 OBS	No	Eight trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82); Observational data are supportive	NA
	• Comparing to truly no prophylaxis	5 RCTs	No	Four trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
	• 2001-present	2 RCTs 1 OBS	No	No events in the groups compared; Observational data suggested no difference	NA
	• THR	5 RCTs	No	Four trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
	• TKR	2 RCTs	No	No events in the groups compared	NA
	• HFS	2 RCTs	No	No events in the groups compared	NA
	Oral antiplatelet agents versus no prophylaxis	2 RCTs	No	No events in the groups compared	NA
	Injectable low molecular weight heparin versus no prophylaxis	6 RCTs 1 OBS	No	Five trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82); Observational data were supportive	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	No events in the groups compared; Observational data suggested no significant difference	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	--
HRQOL	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
DVT	Pharmacologic versus no prophylaxis	17 RCTs	Yes	RR: 0.56 (0.47 to 0.68)†	52.8
	• Comparing to truly no prophylaxis	9 RCTs	Yes	RR: 0.44 (0.27 to 0.72)†	69
	• 2001-present	5 RCTs	Yes	RR: 0.54 (0.45 to 0.64)†	10.4
	• THR	12 RCTs	Yes	RR: 0.59 (0.45 to 0.77)†	52.9
	• TKR	4 RCTs	Yes	RR: 0.54 (0.40 to 0.73)†	61.4
	• HFS	1 RCT	No	RR: 0.35 (0.15 to 0.78)†	---
	• Age	2 RCTs	No	Age did not impact the effect of pharmacologic versus no prophylaxis on the risk of deep vein thrombosis.	NA
	• Gender	2 RCTs	No	1 RCT showed no impact of gender although the other RCT showed decreased risk of DVT in male patients when comparing pharmacologic versus no prophylaxis	NA
	Oral antiplatelet agents versus no prophylaxis	3 RCTs	Yes	RR: 0.41 (0.12 to 1.32)	76
	Injectable low molecular weight heparin versus no prophylaxis	12 RCTs	Yes	RR: 0.54 (0.44 to 0.67)†	50.2
	Injectable unfractionated heparin versus no prophylaxis	1 RCT	No	RR: 1.60 (0.66 to 4.05)	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	RR: 0.99 (0.35 to 2.80)	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.51 (0.37 to 0.69)†	NA
	Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.26 (0.10 to 0.65)†	NA
	Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.26 (0.10 to 0.65)†	NA

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Asymptomatic DVT	Pharmacologic versus no prophylaxis	3 RCTs	Yes	RR 0.52 (0.40 to 0.69)†	32.7
	• 2001-present	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)†	NA
	• THR	2 RCTs	Yes	RR 0.52 (0.27 to 1.00)	NA
	• TKR	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)†	NA
	Injectable low molecular weight heparin versus no prophylaxis	2 RCTs	Yes	RR 0.52 (0.27 to 1.00)	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)†	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Symptomatic DVT	Pharmacologic versus no prophylaxis	4 RCTs 1 OBS	Yes (RCT)	One trial and 1 comparison from one trial had no events; the remaining trials showed OR 1.07 (0.25 to 4.52); observational data suggest no significant difference	0
	• 2001-present	2 RCTs	Yes	1 comparison from one trial had no events; the remaining trials showed RR 1.02 (0.21 to 4.89)	0
	• THR	3 RCTs	Yes	One trial and 1 comparison from one trial had no events; the remaining trials showed OR 1.90 (0.20 to 18.32)	NA
	• TKR	1 RCT (2 comp)	Yes	RR 0.72 (0.12 to 4.39)	NA
	Injectable low molecular weight heparin versus no prophylaxis	3 RCTs	No	Two trials had no events; the remaining trial showed OR 0.96 (0.06 to 15.52)	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	OR: 7.30 (0.14 to 368.00)	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.72 (0.12 to 4.39)	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Proximal DVT	Pharmacologic versus no prophylaxis	12 RCTs	Yes	RR 0.53 (0.39 to 0.74)†	9.7
	• Comparing to truly no prophylaxis	5 RCTs	Yes	RR 0.46 (0.27 to 0.79)†	0
	• 2001-present	5 RCTs	Yes	RR 0.42 (0.22 to 0.79)†	0
	• THR	8 RCTs	Yes	One comparison from one trial had no events; the remaining trials showed RR 0.56 (0.38 to 0.81)†	20.9
	• TKR	4 RCTs	Yes	RR 0.43 (0.21 to 0.88)†	0
	Oral antiplatelet agents versus no prophylaxis	1 RCT	No	RR 0.80 (0.25 to 2.31)	NA
	Injectable low molecular weight heparin versus no prophylaxis	9 RCTs	Yes	1 comparison from one trial had no events; the remaining trials showed RR 0.53 (0.38 to 0.75)†	14.3
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	OR 7.30 (0.14 to 368.00)	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.21 (0.05 to 0.95)†	NA
	Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.41 (0.10 to 1.72)	NA
	Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.41 (0.10 to 1.72)	NA
Distal DVT	Pharmacologic versus no prophylaxis	7 RCTs	Yes	RR 0.59 (0.42 to 0.82)†	0
	• Comparing to truly no prophylaxis	3 RCTs	Yes	RR 0.57 (0.22 to 1.46)	66.8
	• 2001-present	2 RCT	Yes	RR 0.52 (0.20 to 1.38)	48.9
	• THR	5 RCTs	Yes	RR 0.62 (0.42 to 0.90)†	0
	• TKR	2 RCTs	Yes	RR 0.55 (0.10 to 3.19)	NA
	Oral antiplatelet agents versus no prophylaxis	1 RCT	No	RR 1.33 (0.45 to 3.84)	NA
	Injectable low molecular weight heparin versus no prophylaxis	6 RCTs	Yes	RR 0.52 (0.37 to 0.75)†	0
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	RR 0.99 (0.35 to 2.80)	NA
	Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.68 (0.14 to 3.26)	NA
	Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.68 (0.14 to 3.26)	NA

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Major bleeding	Pharmacologic versus no prophylaxis	8 RCTs 1 OBS	Yes (RCT)	Two trials had no events; the remaining trials showed RR 0.74 (0.36 to 1.51); Observational data were supportive	0
	• Comparing to truly no prophylaxis	4 RCTs	Yes	1 trial had no events; the remaining trials showed OR 0.53 (0.17 to 1.64)	0
	• 2001-present	4 RCTs 1 OBS	Yes (RCT)	One trial had no events; the remaining trials showed RR 0.87 (0.31 to 2.45); Observational data were supportive	0
	• THR	5 RCTs	Yes	2 trials had no events; the remaining trials showed OR 1.61 (0.44 to 5.83)	0
	• TKR	2 RCTs	Yes	RR 0.59 (0.18 to 1.95)	0
	• HFS	1 RCT (2 comp)	Yes	RR 0.55 (0.12 to 2.51)	0
	Oral antiplatelet agents versus no prophylaxis	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.24 (0.05 to 1.22)	NA
	Injectable low molecular weight heparin versus no prophylaxis	5 RCTs 1 OBS	Yes	One trial had no events; the remaining trials showed RR 0.78 (0.29 to 2.08); Observational data were supportive	0
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.96 (0.09 to 10.73)	NA
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	No events occurred in the groups compared; Observational data suggested no significant difference	NA
	Oral vitamin K antagonists versus no prophylaxis	1 RCT	No	RR 0.97 (0.29 to 3.19)	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Major bleeding leading to reoperation	Pharmacologic versus no prophylaxis	2 RCTs	No	One trial and one comparison of one trial had no events; the remaining comparison of the second trial showed OR 7.11 (0.14 to 358.50)	NA
	• 2001-present	1 RCT (2 comp)	No	One comparison of the trial had no events; the remaining comparison showed OR 7.11 (0.14 to 358.50)	NA
	• THR	1 RCT	No	No events in the groups compared	NA
	• TKR	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50)	NA
	Injectable low molecular weight heparin versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50)	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Minor bleeding	Pharmacologic prophylaxis versus no prophylaxis	6 RCTs	Yes	RR 1.67 (1.18 to 2.38)†	0
	• Comparing to truly no prophylaxis	1 RCT	No	OR 7.39 (0.15 to 372.38)	NA
	• 2001-present	4 RCTs	Yes	RR 2.04 (1.16 to 3.62)†	0
	• THR	4 RCTs	Yes	RR 1.65 (1.09 to 2.48)†	0
	• TKR	2 RCTs	Yes	RR 1.77 (0.89 to 3.49)	0
	Injectable low molecular weight heparin versus no prophylaxis	5 RCTs	Yes	RR 1.66 (1.13 to 2.44)†	0
	Injectable or oral factor Xa inhibitors versus no prophylaxis	1 RCT (1 comp)	No	OR 3.21 (0.84 to 12.24)	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	OR 1.67 (0.73 to 3.84)	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Surgical site bleeding	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---
Bleeding leading to infection	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---
Bleeding leading to transfusion	Pharmacologic versus no prophylaxis	1 RCT (2 comp) 1 OBS	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50). The observational study was inconclusive.	NA
	• 2001-present	1 RCT (2 comp) 1 OBS	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50). The observational study was inconclusive.	NA
	• TKR	1 RCT (2 comp) 1 OBS	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50). The observational study was inconclusive.	NA
	Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	One comparison of the trial had no events; the remaining comparison showed OR 7.11 (0.14 to 358.50).	NA
	Oral vitamin K antagonists versus no prophylaxis	1 OBS	No	The study was inconclusive	NA
	Mechanical prophylaxis versus no prophylaxis	0	---	---	---
HIT	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---
Discomfort	Pharmacologic versus no prophylaxis	0	---	---	---
	Mechanical versus no prophylaxis	0	---	---	---
Readmission	Pharmacologic versus no prophylaxis	1 OBS	No	No difference in the risk of readmission.	NA
	Oral vitamin K antagonists versus no prophylaxis	1 OBS	No	No difference in the risk of readmission.	NA
	Mechanical versus no prophylaxis	0	---	---	---

Table 10. Summary of results for Key Question 4: what is the comparative efficacy and safety of pharmacologic or mechanical prophylaxis versus no prophylaxis on outcomes in patients who had major orthopedic surgery* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Reoperation	Pharmacologic versus no prophylaxis	1 OBS	No	Significant increase in risk of reoperation in patients who received pharmacologic prophylaxis versus no prophylaxis.	NA
	Oral vitamin K antagonists versus no prophylaxis	1 OBS	No	Significant increase in risk of reoperation in patients who received pharmacologic prophylaxis versus no prophylaxis.	NA
	Mechanical versus no prophylaxis	0	---	---	---

comp = comparison(s); DVT = deep vein thrombosis; HIT = heparin induced thrombocytopenia; HRQOL = health related quality of life; NA = Not Applicable; OBS = observational; OR = Peto's Odds Ratio; PE = pulmonary embolism; RCT = Randomized Controlled Trial; RR = Relative Risk; VTE = venous thromboembolism

*All base case analyses are represented in this table. For subgroup analyses or class comparisons only analyses with trials or studies are represented.

†Statistically significant.

--- No data.

Key Question 5

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists, and mechanical interventions.

Key Points

- Although no difference was found in the base case analysis, when patients with total hip replacement were evaluated separately, injectable low molecular weight heparin agents had significantly fewer objectively confirmed symptomatic venous thromboembolism events versus injectable or oral factor Xa inhibitors.
- Injectable low molecular weight heparin agents had significantly fewer pulmonary embolism events versus injectable unfractionated heparin [OR 0.48 (0.24 to 0.95)].
 - Injectable low molecular weight heparin agents had significantly fewer pulmonary embolism events versus injectable unfractionated heparin in total hip replacement surgery while in hip fracture surgery; injectable low molecular weight heparins had significantly higher pulmonary embolism events versus injectable unfractionated heparin.
- In a controlled observational study, oral vitamin K antagonists had significantly fewer fatal pulmonary embolism events versus oral antiplatelet agents.
 - In the only available randomized controlled trial, the same direction of effect was found but this was not significant.
- Although there was no significant difference between groups at preventing nonfatal pulmonary embolism, injectable low molecular weight heparin was statistically superior versus injectable unfractionated heparin in total hip replacement surgery but statistically inferior in hip fracture surgery.
 - The higher level of statistical heterogeneity in the base case analysis was likely due to the type of surgery.
- Although there was no significant difference between groups at preventing nonfatal pulmonary embolism, injectable low molecular weight heparin was statistically superior to injectable or oral factor Xa inhibitors in total hip replacement surgery.
- While no differences in mortality occurred in the available trials, several observational studies found significant differences.
 - In a controlled observational study, oral antiplatelet agents had significantly higher mortality versus oral vitamin K antagonists in total hip or total knee

- replacement surgeries in one study but another study limited to total knee replacement found no significant differences.
- In a controlled observational study, injectable low molecular weight heparin agents had significantly higher mortality versus injectable or oral factor Xa inhibitors in total hip, knee replacement and hip fracture surgeries. A second study did not find a significant difference between the two groups, also evaluating all three surgery populations.
 - In a controlled observational study, the use of an injectable factor Xa inhibitor was associated with a lower mortality than injectable unfractionated heparin.
 - Oral antiplatelet agents had significantly more deep venous thrombosis events versus mechanical prophylaxis [RR 1.63 (1.11 to 2.39)].
 - Oral antiplatelet agents had significantly more deep venous thrombosis events versus mechanical prophylaxis in total knee replacement surgery.
 - Injectable low molecular weight heparin agents had significantly fewer deep venous thrombosis events versus unfractionated heparin [RR 0.80 (0.65 to 0.99)].
 - Injectable low molecular weight heparin agents had significantly fewer deep venous thrombosis events versus injectable unfractionated heparin in total hip and total knee replacement surgeries.
 - Injectable low molecular weight heparin agents had significantly more deep venous thrombosis events versus injectable unfractionated heparin in hip fracture surgery.
 - No differences in efficacy between injectable low molecular weight or injectable unfractionated heparin was seen based on age, gender, or African American race but enoxaparin 30mg, but not 40mg, was superior to unfractionated heparin in preventing deep venous thrombosis in Caucasians.
 - Injectable low molecular weight heparins had significantly more deep venous thrombosis events versus injectable or oral factor Xa inhibitors [RR 1.99 (1.57 to 2.51)].
 - In studies conducted from 2001-present, the same results occurred.
 - Injectable low molecular weight heparins had significantly more deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total hip replacement, total knee replacement, and hip fracture surgeries.
 - Injectable low molecular weight heparin agents had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors [RR 1.39 (1.15 to 1.68)].
 - Injectable low molecular weight heparins had significantly fewer deep venous thrombosis events versus oral vitamin K antagonists [RR 0.66 (0.55 to 0.79)].
 - There were higher levels of statistical heterogeneity but the direction of effect was similar in all trials.
 - Injectable low molecular weight heparins had significantly fewer deep venous thrombosis events versus oral vitamin K antagonists in trials conducted from 2001-present, total hip replacement and total knee replacement surgeries.
 - Injectable unfractionated heparin had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors [RR 2.31 (1.34 to 4.00)].
 - Injectable unfractionated heparin had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total hip replacement.

- Injectable unfractionated heparin had significantly more deep venous thrombosis events versus mechanical prophylaxis.
- Injectable low molecular weight heparin agents had significantly fewer asymptomatic deep vein thrombosis events versus oral vitamin K antagonists.
 - The same results occurred in trials published from 2001-present and in total knee replacement.
- While no significant differences were seen in the base case analysis, injectable low molecular weight heparin agents had significantly fewer symptomatic deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total hip replacement surgery.
- Injectable low molecular weight heparin agents had significantly fewer proximal deep venous thrombosis events versus injectable unfractionated heparin [RR 0.60 (0.38 to 0.93)].
 - Injectable low molecular weight heparin agents had significantly fewer proximal deep venous thrombosis events versus injectable unfractionated heparin in total hip replacement surgery and total knee replacement surgery.
- Injectable low molecular weight heparin agents had significantly more proximal deep venous thrombosis events versus injectable or oral factor Xa inhibitors [OR 2.19 (1.52 to 3.16)].
 - The same results occurred when limited to studies from 2001-present.
 - There was a higher level of statistical heterogeneity but three of four trials had the same direction of effect. Heterogeneity could not be readily explained by the year of publication or type of surgery.
 - Injectable low molecular weight heparin agents had significantly more proximal deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total knee replacement surgery and hip fracture surgery with a trend in the same direction with total hip replacement surgery.
- While no significant differences occurred in the base case analysis, injectable low molecular weight heparin agents had significantly more proximal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total hip replacement surgery.
- Injectable low molecular weight heparin agents did not significantly impact the risk of proximal deep venous thrombosis versus oral vitamin K antagonists with borderline significance [RR 0.63 (0.37 to 1.00)].
- Injectable unfractionated heparin had significantly more proximal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors [OR 4.74 (2.99 to 7.49)].
 - Injectable unfractionated heparin had significantly more proximal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total hip replacement surgery.
- Oral vitamin K antagonists had significantly fewer proximal deep venous thrombosis events versus mechanical prophylaxis [RR 0.34 (0.16 to 0.73)].
 - Oral vitamin K antagonists had significantly fewer proximal deep venous thrombosis events versus mechanical prophylaxis in total hip replacement surgery.

- Oral antiplatelet agents had significantly more distal deep venous thrombosis events versus mechanical prophylaxis.
 - Oral antiplatelet agents had significantly more distal deep venous thrombosis events versus mechanical prophylaxis in total knee replacement surgery.
- Injectable low molecular weight heparin agents had significantly more distal deep venous thrombosis events versus injectable or oral factor Xa inhibitors [RR 2.02 (1.65 to 2.48)].
 - The same result occurred when limiting to studies from 2001-present.
 - Injectable low molecular weight heparin agents had significantly more distal deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total hip replacement, total knee replacement, and hip fracture surgeries.
- Injectable low molecular weight heparins had significantly fewer distal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors.
 - The same result occurred when limiting to studies from 2001-present.
 - Injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total knee replacement.
- Injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus oral vitamin K antagonists [RR 0.56 (0.43 to 0.73)].
 - The same result occurred when limiting to studies from 2001-present.
 - Injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus oral vitamin K antagonists in total hip replacement and total knee replacement surgeries.
- Injectable low molecular weight heparin agents had significantly less major bleeding than injectable unfractionated heparin [OR 0.57 (0.37 to 0.88)].
 - Injectable low molecular weight heparin agents had significantly less major bleeding than injectable unfractionated heparin in total hip replacement surgery.
- Injectable low molecular weight heparin agents had significantly less major bleeding than injectable or oral factor Xa inhibitors [OR 0.65 (0.48 to 0.89)].
 - The results were the same when limited to trials from 2001-present.
 - Injectable low molecular weight heparin agents had significantly less major bleeding than injectable or oral factor Xa inhibitors in total hip replacement surgery and total knee replacement surgery.
 - The different direction of effect between the total hip and knee replacement surgery trials versus the hip fracture surgery trials likely explains the higher level of statistical heterogeneity in the base case analysis.
- Injectable low molecular weight heparin agents had significantly more major bleeding than oral vitamin K antagonists [OR 1.92 (1.27 to 2.91)].
 - Injectable low molecular weight heparin agents had significantly more major bleeding than oral vitamin K antagonists in total hip replacement surgery and total knee replacement surgery.
- In the only evaluation available (a controlled observational study), major bleeding events were significantly increased in the group receiving injectable unfractionated heparin versus injectable or oral factor Xa inhibitors.
- Injectable low molecular weight heparin agents had significantly less minor bleeding than injectable or oral factor Xa inhibitors [OR 0.57 (0.35 to 0.94)].

- The results were the same when limited to trials from 2001-present.
 - Injectable low molecular weight heparin agents had significantly less minor bleeding than injectable or oral factor Xa inhibitors in hip fracture surgery.
- Injectable low molecular weight heparin agents had significantly more minor bleeding than oral vitamin K antagonists [RR 1.23 (1.06 to 1.43)].
- Injectable low molecular weight heparin agents had significantly more surgical site bleeding than injectable or oral direct thrombin inhibitors.
 - The same results occurred when trials were limited to 2001-present.
 - Injectable low molecular weight heparin agents had significantly more surgical site bleeding than injectable or oral direct thrombin inhibitors in total knee replacement surgery.
- Injectable low molecular weight heparin agents had significantly more surgical site bleeding than oral vitamin K antagonists [OR 2.63 (1.31 to 5.28)].
 - Injectable low molecular weight heparin agents had significantly more surgical site bleeding than oral vitamin K antagonists in total hip replacement surgery.
 - When major surgical site bleeding was evaluated for separately, injectable low molecular weight heparin agents had significantly more major surgical site bleeding than oral vitamin K antagonists.
- Injectable low molecular weight heparin agents had significantly less heparin induced thrombocytopenia than injectable unfractionated heparin [OR 0.12 (0.03 to 0.43)].
 - Injectable low molecular weight heparin agents had significantly less heparin induced thrombocytopenia than injectable unfractionated heparin in total hip replacement surgery.
- Injectable low molecular weight heparin agents had significantly less discomfort than mechanical prophylaxis.
 - Injectable low molecular weight heparin agents had significantly less discomfort than mechanical prophylaxis in total hip replacement surgery.

Detailed Analysis

Study Design and Characteristics

Forty-five randomized controlled trials (N=36,152) and three controlled observational studies (N=144,806) evaluated the comparative efficacy between classes of pharmacologic prophylaxis and mechanical methods of prophylaxis on final health, intermediate and adverse outcomes.^{55-58,60-69,71,73-77,79-86,88-90,93-99,101,102,104-106,132,135} All forty-five randomized controlled trials were published as full text manuscripts. Two randomized controlled trials compared oral antiplatelet agents to oral vitamin K antagonists^{88,132} and two trials compared oral antiplatelet agents to mechanical methods of prophylaxis.^{79,82} Fourteen trials compared injectable low molecular weight heparins to injectable unfractionated heparin,^{55,57,61-63,71,74,86,89,93,96,97,104,105} six trials compared injectable low molecular weight heparin to injectable or oral factor Xa inhibitors,^{58,64,83,99,106,135} five trials compared injectable low molecular weight heparins to injectable or oral direct thrombin inhibitors,^{65-67,73,94} seven trials compared injectable low molecular weight heparins to oral vitamin K antagonist^{60,75,77,80,81,84,85} and three trials compared injectable low molecular weight heparin to mechanical prophylaxis.^{98,101,102} Two trials compared injectable unfractionated heparin to injectable or oral direct thrombin inhibitors^{68,69} and one trial

compared injectable unfractionated heparin to mechanical prophylaxis.⁹⁵ Three trials compared oral vitamin K antagonists to mechanical prophylaxis.^{56,76,90}

Twenty-six trials enrolled exclusively patients who had total hip replacement surgery (N=20,261),^{55-57,60,61,63,67-69,71,73,76,77,81,83,86,89,90,93,95-99,101,135} eleven trials enrolled patients who had total knee replacement surgery (N=8,185),^{58,62,66,74,75,79,84,85,94,101,106} four trials enrolled patients who had hip fracture surgery (N=2,155).^{64,82,105,132} and four trials enrolled patients who had either total hip replacement surgery or total knee replacement surgery (N=4,043).^{65,80,88,104} The earliest trial was published in 1987 while the most recent published in 2011.^{57,90,135} The duration of followup ranged from the postoperative period to 180 days. Seven randomized controlled trials reported outcomes of interest during the postdischarge period.^{61,69,74,80,94,97} Seventeen trials received funding from industry,^{56,60,61,64-67,73-75,83,85,89,94,97,99,106} six trials received funding from government and foundation,^{71,76,80,86,88,101} one trial received funding from industry and government,¹³² one trial received funding from academia and industry,⁸¹ two trials received funding from industry, government and foundation^{90,132} and in nineteen trials the funding source was not reported.^{55,57,58,62,63,68,69,77,79,82,84,93,95,96,98,102,104,105,135}

The mean age of enrolled patients ranged from 52.4 years to 78.3 years. Females represented between 36.05 and 84.09 percent of the enrolled populations. The mean weight ranged from 64.2 to 89 kilograms and obesity ranged from 5.4 to 59.09 percent. Few patients enrolled had a history of venous thromboembolism ranging from 0 to 14.49 percent. Presence of varicosity ranged from no varicosity to 55 percent. The percent of patients with a history of malignancy ranged from 0 to 12.4 percent. The percent of patients who had previously undergone orthopedic surgery ranged from 4 to 52.24 percent.

Fifty-four to 100 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 21.2 to 100 percent. Mean duration of surgery ranged from 59 to 172 minutes and the mean duration of anesthesia was reported by four trials with a range of 127 to 205 minutes. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 0 to 100 percent of patients and regional anesthesia use also ranging from 0 to 100 percent of patients. The mean length of hospital stay was infrequently reported, and when it was ranged from 9 to 17.2 days.

Of the three observational studies, two studies compared oral antiplatelet agents to oral vitamin K antagonists^{144,148} and one study reported comparison between injectable low molecular weight heparin, injectable unfractionated heparin and injectable or oral factor Xa inhibitors.¹⁴⁷ One study enrolled only patients who had total knee replacement surgery (N=93,840)¹⁴⁸ and another evaluated two surgical procedures and reported the outcomes separately for each; total hip replacement (N=2,203) and total knee replacement surgery (N=2,050).¹⁴⁴ The third study enrolled patients who had total hip replacement, total knee replacement, or hip fracture surgery (N=144,806).¹⁴⁷ The most recent study was published in 2010 while the earliest study was published in 2007. The duration of followup for the studies ranged from 30 to 90 days. One study was funded by government and foundation¹⁴⁸ while the other two did not disclose the funding source.^{144,147}

The mean age of patients ranged from 66.4 to 71 years. Females represented between 63.0 to 65.17 percent of the enrolled populations. Other baseline characteristics were not reported. Two studies enrolled exclusively patients who had primary surgery.^{144,148} One study reported the surgical approach and for those who had total hip replacement, the posterior approach was used while for those who had total knee replacement the medial parapatellar approach was used.¹⁴⁴

Median hospital length of stay was reported in one study as 3 days.¹⁴⁸ Other procedural characteristics were not reported in these three studies.

Outcome Evaluations

Outcomes reported during the postdischarge period are analyzed and reported separately within the corresponding class comparison section under the respective outcome. A summary of significant differences between comparative groups for outcomes in base case and subgroup analyses is presented in Table 11 and an overall summary of results presented in Table 12.

One trial by Eriksson and colleagues in 2005 was a dose finding study that evaluated the impact of four dabigatran doses (50mg twice daily, 150mg twice daily, 300mg daily or 225mg twice daily) versus enoxaparin on various outcomes of interest in patients who had either total hip or total knee replacement surgery.⁶⁵ When pooling trials that evaluated dabigatran in this report, the doses that have been evaluated in phase 3 trials were analyzed since dabigatran did not yet have Food and Drug Administration approval for venous thromboembolism. In this dose finding study, none of the regimens were those studied in phase 3 trials, and given the paucity of data comparing dabigatran to injectable low molecular weight heparin agents, the outcomes evaluated in this trial were discussed qualitatively.

Symptomatic Objectively Confirmed Venous Thromboembolism

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.⁹⁷ In this trial by Senaran and colleagues in 2006, patients who had total hip replacement surgery were randomized to receive either enoxaparin or unfractionated heparin prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 0.13 (0.01 to 2.15)]. Subgroup analyses were not possible because only one trial was available.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic objectively confirmed venous thromboembolism during the postdischarge period in patients who had total hip replacement surgery.⁹⁷ In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the odds of symptomatic objectively confirmed

venous thromboembolism during the postdischarge period were not significantly different [OR 7.54 (0.47 to 122.28)].

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.^{64,83,99,106,135} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 0.70 (0.48 to 1.02)] (Appendix G Figure 59). A lower level of statistical heterogeneity was detected and publication bias was not detected ($I^2=38.5$ percent, Egger's p -value=0.895). This is the same result obtained when limiting the analysis to trials published from 2001-present since all five trials fit this criterion. When limiting the original analysis to total hip replacement surgery three trials remained.^{83,99,135} In patients with total hip replacement surgery who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the odds of symptomatic objectively confirmed venous thromboembolism were significantly decreased [OR 0.53 (0.32 to 0.87), NNT 50 to 100] (Appendix G Figure 60). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 1.97 (0.71 to 5.45)]. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 0.75 (0.37 to 1.55)].

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.^{60,85} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 1.00 (0.69 to 1.46)] (Appendix G Figure 61). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

Subgroup analysis based on trials published from 2001-present was not possible since both trials were published prior to 2001. When limiting the original analysis to total hip replacement surgery one trial remained.⁶⁰ In this trial, in patients who received injectable low molecular

weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 0.97 (0.66 to 1.41)]. When limiting the original analysis to total knee replacement surgery one trial remained.⁸⁵ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 2.71 (0.38 to 19.35)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on symptomatic objectively confirmed venous thromboembolism during the postdischarge period in patients who had major orthopedic surgery.⁸⁰ This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism during the postdischarge period were not significantly different [OR 2.24 (0.65 to 7.79)] (Appendix G Figure 62). Similar results were seen when evaluating total hip replacement surgery [OR 2.74 (0.68 to 11.01)] or total knee replacement surgery [OR 1.02 (0.06 to 16.38)] separately.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Major Venous Thromboembolism

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major venous thromboembolism in patients who had major orthopedic surgery.^{66,67} Two trials by Eriksson and colleagues each provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.26 (0.98 to 1.62)] (Appendix G Figure 63). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.326).

When limiting the original analysis to trials published from 2001-present, two trials remained each including two separate comparisons.^{66,67} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.08 (0.78 to 1.50)] (Appendix G Figure 64). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement surgery two trials remained with one including two separate comparisons.^{67,69} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.28 (0.94 to 1.76)] (Appendix G Figure 65). A lower level of statistical heterogeneity was detected ($I^2=18.6$ percent). When limiting the original analysis to total knee replacement surgery one trial which included two separate comparisons remained.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of

major venous thromboembolism was not significantly different [RR 1.11 (0.63 to 1.96)] (Appendix G Figure 66). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Pulmonary Embolism

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.¹³² In this trial by Powers and colleagues in 1989, patients who had hip fracture surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis the odds

of pulmonary embolism were not significantly different [OR 7.28 (0.14 to 366.83)]. Subgroup analyses were not possible since this was the only trial available.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.⁸² In this trial by Kennedy and colleagues in 2000, patients who had hip fracture surgery were randomized to receive either aspirin or venous foot pump prophylaxis. In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis the odds of pulmonary embolism were not significantly different [OR 7.09 (0.14 to 357.70)]. Subgroup analyses were not possible since this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on pulmonary embolism in patients who had major orthopedic surgery and one trial included two separate comparisons.^{55,57,61,62,71,74,86,96,97,105} Four trials were excluded from the analysis because no events occurred in the groups compared.^{57,74,96,97} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.48 (0.24 to 0.95), NNT 8] (Appendix G Figure 67). A range could not be calculated for the NNT because the lowest control event rate was zero. A higher level of statistical heterogeneity was detected although publication bias was not detected ($I^2=59.7$ percent, Egger's p -value=0.623). The direction of effect was similar in all trials and showed nonsignificant difference except for one trial. Heterogeneity, then, is likely due to differences in the magnitude of benefit.

When limiting the original analysis to trials published from 2001-present one trial remained although no events occurred therefore the risk of pulmonary embolism could not be calculated.⁹⁷ When limiting the original analysis to total hip replacement surgery seven trials remained with one trial including two separate comparisons.^{55,57,61,71,86,96,97} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.28 (0.13 to 0.62), NNT 8] (Appendix G Figure 68). A range could not be calculated for the NNT because the lowest control event rate was zero. Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery two trials remained.^{62,74} One trial was excluded because no events occurred.⁷⁴ In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.13)]. When limiting the original analysis to hip fracture surgery one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly increased [OR 7.95 (1.53 to 41.29)]. The NNT could not be calculated because the control event rate was zero. Statistical heterogeneity could not be evaluated because of too few studies.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on pulmonary

embolism during the postdischarge period in patients who had total hip replacement surgery.⁶¹ This trial included two comparisons; enoxaparin 30mg every 12 hours or enoxaparin 40mg daily versus unfractionated heparin. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of pulmonary embolism during the postdischarge period was not significantly different [RR 0.13 (0.01 to 1.17)] (Appendix G Figure 69).

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.^{106,135} One trial by Yokote and colleagues was excluded because no events occurred in either of the treatment arms leaving only one trial by Bauer and colleagues in 2001. In this trial by Bauer and colleagues, patients who had total knee replacement surgery were randomized to receive enoxaparin or fondaparinux prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of pulmonary embolism were not significantly different [OR 3.34 (0.58 to 19.32)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.^{66,67 69} Two trials by Eriksson and colleagues each provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 1.18 (0.41 to 3.39)] (Appendix G Figure 70). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.208).

When limiting the original analysis to trials published from 2001-present, two trials remained with each including two separate comparisons.^{66,67} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of pulmonary embolism was not significantly different [RR 1.25 (0.35 to 4.39)] (Appendix G Figure 71). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement surgery two trials remained with one including two separate comparisons.^{67,69} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 1.03 (0.32 to 3.36)] (Appendix G Figure 72). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one trial which included two separate comparisons remained.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 2.00 (0.18 to 22.02)] (Appendix G Figure 73). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on pulmonary embolism during the post discharge period in patients who had total hip replacement surgery.⁷³ In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of pulmonary embolism during the post discharge period were not significantly different [OR 3.89 (0.78 to 19.34)].

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Five randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.^{60,75,81,84,85} One trial included two separate comparisons although it was excluded from the analysis because no events occurred in the groups compared.⁸¹ In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.11 (0.57 to 2.19)] (Appendix G Figure 74). A lower level of statistical heterogeneity was detected although the presence of publication bias was not detected ($I^2=28.7$ percent, Egger's p-value=0.762).

When limiting the original analysis to trials published from 2001-present two trials remained.^{75,84} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.96 (0.20 to 18.94)] (Appendix G Figure 75). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery two trials remained with one trial including two separate comparisons, although this latter trial was excluded because no events occurred in the groups compared.^{60,81} In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.23 (0.58 to 2.63)]. When limiting the original analysis to total knee replacement surgery three trials remained.^{75,84,85} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.75 (0.17 to 3.31)] (Appendix G Figure 76). A lower level of statistical heterogeneity was detected ($I^2=48.2$ percent). Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery.⁸⁰ This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism during the postdischarge period were not significantly different [OR 1.01 (0.06 to 16.14)] (Appendix G Figure 77). Similar results were seen when evaluating total hip replacement surgery [OR 7.37 (0.15 to 371.45)] or total knee replacement surgery [OR 0.14 (0.003 to 6.97)] separately.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.¹⁰¹ In this trial by Warwick and colleagues in 1998, patients who had total hip replacement surgery were randomized to receive enoxaparin or venous foot pump prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.72)]. Subgroup analyses were not possible because this was the only trial available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on pulmonary embolism in patients who had major orthopedic surgery.^{68,69} In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of pulmonary embolism were not significantly different [OR 3.27 (0.56 to 18.98)] (Appendix G Figure 78). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery as both trials evaluated this surgical population. Subgroup analysis based on trials published from 2001-present was not possible as both trials were published prior to 2001. Subgroup analyses based on total knee replacement or hip fracture surgery were not possible as no trials evaluated these surgical populations.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery although no events occurred therefore the risk of pulmonary embolism could not be calculated.⁹⁰

Fatal Pulmonary Embolism

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major

orthopedic surgery.¹³² This trial by Powers and colleagues in 1989 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.28 (0.14 to 366.83)]. Subgroup analyses were not possible as only one trial was available.

One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.¹⁴⁴ This study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis. A significantly higher percent of patients who received aspirin prophylaxis had a fatal pulmonary embolism compared with those who received warfarin prophylaxis (0.07 percent versus 0 percent, $p < 0.05$).

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{57,61,62,71,74,86,93,96,97,105} Nine trials were excluded from the analysis because no events occurred in the groups compared.^{57,61,71,74,86,93,96,97,105} The remaining trial by Colwell and colleagues in 1995 evaluated patients who had total knee replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.73)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{64,83,99,106,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment arms; therefore four trials were included in the meta-analysis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.90 (0.38 to 2.13)] (Appendix G Figure 79). Statistical heterogeneity and publication bias were not detected ($I^2 = 0$ percent, Egger's p -value = 0.744). This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery three trials remained.^{83,99,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment arms, therefore only two trials were included in this meta-analysis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.00 (0.14 to 7.10)] (Appendix G Figure 80). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original

analysis to total knee replacement surgery, one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.00 (0.06 to 16.01)]. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.87 (0.31 to 2.39)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{66,67} The trials by Eriksson and colleagues in 2007 both provided two separate comparisons.^{66,67} One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total hip replacement was excluded from the analysis because no events occurred in either group.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.43 (0.08 to 24.82) (Appendix G Figure 81). A lower level of statistical heterogeneity was detected ($I^2=31.7$ percent), but publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained that provided two separate comparisons, one comparison was excluded from the analysis because no events occurred in either group.⁶⁷ In the remaining comparison, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.91)]. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of fatal pulmonary embolism was not significantly different [RR 4.00 (0.36 to 44.03)] (Appendix G Figure 82). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery.⁷³ In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of fatal pulmonary embolism during the postdischarge period were not significantly different [OR 0.14 (0.003 to 6.97)].

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{60,80,84,85} Three trials were excluded from the analysis because no events occurred in either group.^{80,84,85} The remaining trial by Colwell and colleagues in 1994 evaluated patients who had total hip replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.29 (0.14 to 367.30)]. Subgroup analyses were not possible as only one trial with events was available.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.⁸⁰

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.^{101,102} One trial was excluded from the analysis because no events occurred in either group compared.¹⁰¹ The remaining trial by Warwick and colleagues in 2002 evaluated patients who had total knee replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.25)]. Subgroup analyses were not possible as only one trial with events was available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin prophylaxis versus oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery although no events occurred in either trial so the risk of fatal pulmonary embolism could not be evaluated.^{68 69}

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery

although no events occurred in either group so the risk of fatal pulmonary embolism could not be evaluated.⁹⁰

Nonfatal Pulmonary Embolism

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet agent prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery. However, no events occurred in either group and the risk of nonfatal pulmonary embolism could not be evaluated.¹³²

One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.¹⁴⁴ This study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis. There was no significant difference in the percent of patients who had a nonfatal pulmonary embolism comparing aspirin to warfarin prophylaxis (0.67 percent versus 0 percent, $p=0.112$).

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{57,61,62,71,74,86,93,96,97,105} Four trials were excluded from the analysis because no events occurred in the groups compared.^{57,74,96,97} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.50 (0.25 to 1.00)] (Appendix G Figure 83). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=58.8$ percent, Egger's p -value=0.634). The direction of effect was similar in all trials and showed nonsignificant difference except for one trial. Heterogeneity, then, is likely due to differences in the magnitude of benefit. When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared therefore the risk of nonfatal pulmonary embolism could not be evaluated.⁹⁷ When limiting the original analysis to total hip replacement surgery seven trials remained.^{57,61,71,86,93,96,97} Three trials were excluded from the analysis because no events occurred in the groups compared.^{57,96,97} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.28 (0.13 to 0.62), NNT 6] (Appendix G Figure 84). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery two trials remained.^{62,74} One trial was excluded from the analysis because no events occurred in either group compared.⁷⁴ In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin

prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.73)]. When limiting the original analysis to hip fracture surgery one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were significantly increased [OR 7.95 (1.53 to 41.29)]. The number needed to harm could not be calculated because the control event rate was zero.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on nonfatal pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery.⁶¹ In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin 30mg every 12 hours, enoxaparin 40mg daily or unfractionated heparin prophylaxis. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of nonfatal pulmonary embolism during the postdischarge period was not significantly different [RR 0.13 (0.01 to 1.17)] (Appendix G Figure 69).

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{64,83,99,106,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment groups, therefore four trials were included in the meta-analysis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.68 (0.34 to 1.37)] (Appendix G Figure 85). A lower level of statistical heterogeneity was detected as was the presence of publication bias for studies in which the odds of nonfatal pulmonary embolism were decreased with low molecular weight heparin compared with Xa inhibitors ($I^2=49.5$ percent, Egger's p-value=0.040). This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery three trials remained.^{83,99,135} of which one trial by Yokote and colleagues in 2011 was excluded from the analysis because no events occurred in either of the treatment groups. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.39 (0.16 to 0.95), NNT 166] (Appendix G Figure 86). A range for the NNT could not be calculated since the lower bound of the control event rate was zero. Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.95 (0.39 to 9.72)]. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.32 (0.30 to 5.81)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery, and both trials included two separate comparisons.^{66,67} One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total knee replacement was excluded from the analysis because no events occurred in either group.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.92 (0.23 to 3.66)] (Appendix G Figure 87). A higher level of statistical heterogeneity was detected ($I^2=53.7$ percent), but publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained that included two separate comparisons.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 1.61 (0.13 to 19.37)] (Appendix G Figure 88). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained.⁶⁶ One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total knee replacement was excluded from the analysis because no events occurred in either group.⁶⁶ In the remaining comparison, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.93)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Three randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{80,84,85} The trial by Hull and colleagues in 1993 provided two separate comparisons, however the trial was excluded from the analysis because no events occurred in either comparison.⁸⁰ In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.00 (0.20 to 4.95)] (Appendix G Figure 89). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present one trial remained.⁸⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary

embolism were not significantly different [OR 7.46 (0.46 to 120.00)]. When limiting the original analysis to total hip replacement surgery one trial, contributing two separate comparisons remained, however no events occurred in any of the groups compared therefore the risk of nonfatal pulmonary embolism could not be calculated.⁸⁰ When limiting the original analysis to total knee replacement, two trials remained.^{84,85} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.00 (0.20 to 4.95)] (Appendix G Figure 90). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery.⁸⁰ This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism during the postdischarge period were not significantly different [OR 1.01 (0.06 to 16.14)] (Appendix G Figure 91). Similar results were seen when evaluating total hip replacement surgery [OR 7.37 (0.15 to 371.45)] or total knee replacement surgery [OR 0.14 (0.003 to 6.97)] separately.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

One randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.¹⁰¹ In this trial by Warwick and colleagues in 1998, patients who had total hip replacement surgery were evaluated. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.72)]. Subgroup analyses were not possible as only one trial was available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin prophylaxis versus oral direct thrombin inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{68,69} In patients who received injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 3.27 (0.56 to 18.98)] (Appendix G Figure 92). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result for trials limited to total hip replacement surgery. Subgroup analysis based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery was not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery although no events occurred in either group so the risk of nonfatal pulmonary embolism could not be evaluated.⁹⁰

Post Thrombotic Syndrome

No randomized controlled trials or controlled observational studies compared between pharmacological and/or mechanical classes of prophylaxis to evaluate this outcome.

Mortality

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on mortality in patients who had major orthopedic surgery.¹³² In this trial by Powers and colleagues in 1989, patients who had hip fracture surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of mortality was not significantly different [RR 0.98 (0.32 to 3.05)]. Subgroup analyses were not possible as this was the only trial available.

Two controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on mortality in patients who had major orthopedic surgery.^{144,148} The first study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis.¹⁴⁴ A significantly higher percent of patients who received aspirin prophylaxis died compared with those who received warfarin prophylaxis (0.3 percent versus 0 percent, $p=0.013$). The second study evaluated patients who had total knee replacement surgery and who received either aspirin or warfarin prophylaxis.¹⁴⁸ The odds of mortality for patients who received warfarin versus aspirin prophylaxis were not significantly different [AOR 0.54 (0.25 to 1.15)].

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Eight randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus injectable unfractionated heparin on mortality in patients who had major orthopedic surgery with one trial by Colwell and colleagues including two separate comparisons.^{57,61,71,86,93,96,97,105} Five trials were excluded from the analysis because no events occurred in the groups compared.^{57,86,93,96,97} In patients who received injectable low molecular weight heparins versus injectable unfractionated heparin the odds of mortality were not significantly different [OR 0.39 (0.10 to 1.49)] (Appendix G Figure 93). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.102).

When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared therefore risk of mortality could not be calculated.⁹⁷ When limiting the original analysis to total hip replacement surgery, seven trials remained, with the trial by Colwell and colleagues including two separate comparisons. Five trials were excluded from the analysis because no events occurred in the groups compared. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the odds of mortality in the two remaining trials were not significantly different [OR 0.21 (0.03 to 1.59)] (Appendix G Figure 94). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis based on total knee replacement was not possible because no trials evaluated this surgical population. When limiting the original analysis to hip fracture surgery, one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of mortality was not significantly different [RR 0.64 (0.13 to 3.06)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on mortality in patients who had major orthopedic surgery.^{64,83,99,106,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment arms. In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.08 (0.72 to 1.60)] (Appendix G Figure 95). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.952). This is the same result obtained when limiting the analysis to trials published from 2001-present since all four trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, three trials remained.^{83,99,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment arms. In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 0.88 (0.32 to 2.42)] (Appendix G Figure 96). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial remained.¹⁰⁶ In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.49 (0.26 to 8.65)]. When limiting the original analysis to hip fracture surgery, one trial remained.⁶⁴ In patients who received injectable

low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.10 (0.70 to 1.72)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Two controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery.^{147,150} The first study by Shorr and colleagues in 2007 evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either an injectable low molecular weight heparin (enoxaparin or dalteparin) or fondaparinux. Mortality was significantly decreased in patients who received fondaparinux (0.6 percent) versus injectable low molecular weight heparin (1.1 percent) ($p < 0.001$). The second study by Gerkens and colleagues in 2010 also evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either enoxaparin or fondaparinux prophylaxis. Mortality was not significantly different between the two groups (2.2 percent versus 0.8 percent, respectively, $p = 0.461$).

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on mortality in patients who had major orthopedic surgery with one trial by Ginsberg and two trials by Eriksson and colleagues including two separate comparisons.^{66,94} In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.45 (0.15 to 1.36)] (Appendix G Figure 97). Statistical heterogeneity was not detected ($I^2 = 0$ percent). The presence of publication bias was detected (Egger's p -value = 0.023) although the directionality of the publication bias was unclear.

When limiting the original analysis to trials published from 2001-present, three trials remained with all three trials including two separate comparisons.^{66,67,94} In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.54 (0.15 to 1.98)] (Appendix G Figure 98). Statistical heterogeneity was not detected ($I^2 = 0$ percent). When limiting the original analysis to total hip replacement surgery, two trials remained with one trial by Eriksson and colleagues in 2007 including two separate comparisons.^{67,73} In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.27 (0.06 to 1.23)] (Appendix G Figure 99). Statistical heterogeneity was not detected ($I^2 = 0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained with both trials including two separate comparisons.^{66,94} In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.80 (0.16 to 4.17)] (Appendix G Figure 100). Statistical heterogeneity was not detected ($I^2 = 0$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared with enoxaparin in patients who had total hip or total knee replacement surgery.⁶⁵ During the treatment period, no deaths occurred in any of the groups however during the post

treatment period, one death occurred in each of the dabigatran 50mg twice daily and dabigatran 225mg twice daily groups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Six randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on mortality in patients who had major orthopedic surgery with one trial by Hull and colleagues including two separate comparisons.^{60,75,80,81,84,85} One trial was excluded from the analysis because no events occurred in the groups compared.⁸⁴ In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.79 (0.42 to 1.50)] (Appendix G Figure 101). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.188)

When limiting the original analysis to trials published from 2001-present, two trials remained.^{75,84} One trial was excluded from the analysis because no events occurred in the groups compared⁸⁴ leaving one trial for the analysis. In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.37 (0.05 to 2.66)]. When limiting the original analysis to total hip replacement surgery, two trials remained with one trial by Hull and colleagues including two separate comparisons.^{60,81} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of mortality was not significantly different [RR 0.81 (0.36 to 1.82)] (Appendix G Figure 102). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, three trials remained.^{75,84,85} One trial was excluded from the analysis because no events occurred in the groups compared.⁸⁴ In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.52 (0.10 to 2.57)] (Appendix G Figure 103). Statistical heterogeneity was not evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.^{101,102} In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR 0.31 (0.05 to 1.81)] (Appendix G Figure 104). Statistical heterogeneity and publication bias were not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.¹⁰² In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR 0.38 (0.05 to 2.73)]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.¹⁰¹ In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR

0.14 (0.003 to 7.01)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on mortality in patients who had major orthopedic surgery.^{68,69} In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of mortality were not significantly different [OR 7.13 (0.74 to 68.80)] (Appendix G Figure 105). Statistical heterogeneity and publication bias were not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery and hip fracture surgery were not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

One controlled observational study evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery.¹⁴⁷ This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either fondaparinux or injectable unfractionated heparin. Mortality was significantly decreased in patients who received fondaparinux (0.6 percent) versus injectable unfractionated heparin (2.2 percent) ($p < 0.001$ for both comparisons).

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.⁹⁵ In this trial by Santori and colleagues in 1994, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or venous foot pump prophylaxis. In patients who received injectable unfractionated heparin versus mechanical prophylaxis, the odds of mortality were not significantly different [OR 7.62 (0.15 to 384.19)]. Subgroup analyses were not possible as this was the only trial available.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.^{56,76} One trial was excluded from the analysis because no events occurred in the groups compared,⁵⁶ leaving the trial by Francis and colleagues in 1992.⁷⁶ In this trial, patients who had total hip replacement surgery were randomized to receive either warfarin or intermittent pneumatic compression prophylaxis. In patients who received oral vitamin K antagonist prophylaxis versus mechanical prophylaxis, the odds of mortality were not significantly different [OR 0.95 (0.06 to 15.33)]. Subgroup analyses were not possible as this was the only trial available.

Mortality Due to Bleeding

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery, however no events occurred and therefore the risk of mortality due to bleeding could not be calculated.¹³²

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{57,71,86,93,96,97,105} Six trials were excluded from the pooled analysis because no events occurred in the groups compared.^{57,71,86,93,96,97} The remaining trial by Monreal and colleagues in 1989 evaluated patients who had hip fracture surgery.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.13 (0.003 to 6.52)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{64,83,99,106,135} Four trials were excluded from the pooled analysis because no events occurred in the groups compared.^{83,99,106,135} The remaining trial by Eriksson and colleagues in 2001 evaluated patients who had hip fracture surgery.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 7.29 (0.14 to 367.58)]. Subgroup analyses were not possible because only one trial with events was available.

One controlled observational study evaluated the impact of injectable low molecular weight heparin versus oral or injectable factor Xa inhibitors in major orthopedic surgery.¹⁵⁰ In this study patients who had total hip or knee replacement or hip fracture surgery received either enoxaparin or fondaparinux prophylaxis. Mortality due to bleeding was not significantly different between the groups (0.3 percent versus 0.0 percent, respectively, $p=0.751$).

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{66,67,94} Each trial included two

separate comparisons, although two trials were excluded from the analysis because no events occurred in the groups compared.^{66,94} The remaining trial by Eriksson and colleagues in 2007 evaluated patients who had total hip replacement surgery and included two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of mortality due to bleeding was not significantly different [RR 0.67 (0.07 to 6.40)] (Appendix G Figure 106). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the original analysis to trials published from 2001-present as well as limiting the original analysis to total hip replacement surgery (Appendix G Figure 107). No events occurred in the two trials evaluating patients who had total knee replacement surgery,^{66,94} and no trials evaluated patients who had hip fracture surgery.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{75,80,81,85} One trial included patients who had hip replacement or knee replacement surgery and presented outcomes separately for each surgery while another trial included two comparisons. However, both of these trials, along with a third, were excluded from the analysis because no events occurred in the groups compared.^{80,81,85} The remaining trial by Fitzgerald and colleagues in 2001 evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.94)] in this trial. Subgroup analyses were not possible because only one trial with events was available.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery.^{101,102} One trial was excluded from the analysis because no events occurred in the groups compared, leaving one trial by Warwick and colleagues in 1998 that evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 7.01)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on mortality due to bleeding in patients who had major orthopedic surgery.^{68,69} The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis on mortality due to bleeding. Since no events occurred in the groups compared, the risk of mortality due to bleeding could not be calculated.⁹⁵

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.^{56,76} The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

Health-Related Quality of Life

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between classes of prophylaxis in patients who had major orthopedic surgery on this outcome.

Deep Vein Thrombosis

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on deep vein thrombosis in patients who had major orthopedic surgery.⁸⁸ In this trial by Lotke and colleagues in 1996, patients who had total hip replacement or total knee replacement surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.06 (0.87 to 1.30)]. Subgroup analyses were not possible as this was the only trial available. This trial also evaluated the impact of gender on the development of deep vein thrombosis in patients treated with aspirin or warfarin prophylaxis and reported no significant differences between males and females.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery with one trial by Hass and colleagues including two surgical populations; unilateral or bilateral total knee replacement.^{79,82} In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 1.63 (1.11 to 2.39), NNH 4 to 27] (Appendix G Figure 108). Statistical heterogeneity was not detected ($I^2=0$ percent) and publication bias could not be evaluated because of too few studies.

Subgroup analyses based on trials published from 2001-present or total hip replacement surgery were not possible because no trials fit either of these criteria. When limiting the original analysis to total knee replacement surgery, one trial by Haas and colleagues which reported unilateral and bilateral total knee replacement surgery separately remained.⁷⁹ In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein

thrombosis was significantly increased [RR 1.63 (1.08 to 2.44), NNH 4 to 8] (Appendix G Figure 109). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.⁸² In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.68 (0.55 to 5.19)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Fourteen randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on deep vein thrombosis in patients who had major orthopedic surgery with three trials including two separate comparisons.^{55,57,61-63,71,74,86,89,93,96,97,104,105} The trial by Rader and colleagues was excluded from the pooled analysis because all patients received heparin prophylaxis pre- and postoperatively prior to being randomized to receive enoxaparin or unfractionated heparin.¹⁰⁴ When pooling the remaining thirteen trials, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.80 (0.65 to 0.99), NNT 12 to 100] (Appendix G Figure 110). A lower level of statistical heterogeneity was detected although publication bias was not detected ($I^2=34.3$ percent, Egger's p -value=0.808).

The trial by Rader and colleagues in 1998 that was excluded from the pooled analysis was evaluated separately.¹⁰⁴ This trial evaluated patients who had total hip or total knee replacement surgery and reported outcomes separately. In patients who received injectable low molecular weight prophylaxis versus injectable unfractionated heparin prophylaxis the risk of deep vein thrombosis was not significantly different [RR 3.37 (0.70 to 16.17)] (Appendix G Figure 111). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Results were similar when evaluating the two surgical populations separately; total hip replacement [RR 1.60 (0.21 to 12.06)] and total knee replacement [RR 6.00 (0.99 to 37.43)].

When limiting the original pooled analysis of 13 trials to trials published from 2001-present, 1 trial remained.⁹⁷ In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of deep vein thrombosis were not significantly different [OR 0.13 (0.01 to 2.15)]. When limiting the original analysis to total hip replacement surgery, 10 trials remained, with 3 of the trials including two separate comparisons.^{55,57,61,63,71,86,89,93,96,97} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.75 (0.58 to 0.97), NNT 12 to 100] (Appendix G Figure 112). A lower level of statistical heterogeneity was detected ($I^2=26.4$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained.^{62,74} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.75 (0.58 to 0.96), NNT 12 to 16] (Appendix G Figure 113). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of deep vein thrombosis was significantly increased [RR 2.19 (1.01 to 4.98), NNH 5].

One trial that compared low molecular weight heparin to unfractionated heparin evaluated the impact of age, gender, and ethnicity on deep vein thrombosis.⁶¹ No significant difference in the risk of deep vein thrombosis were found in patients who received low molecular weight heparin versus unfractionated heparin when evaluating those with an age less than 65 years, greater than 65 years, female gender, male gender, or black race. In patients of white race and randomized to enoxaparin 30mg twice daily versus unfractionated heparin, the risk of deep vein thrombosis was significantly decreased (5 percent vs. 14 percent, $p=0.03$) although this effect was not seen when comparing enoxaparin 40mg daily to unfractionated heparin. Although the race categories of “Oriental/Asian” and “other” were also evaluated, risk could not be calculated because no events occurred in the groups compared. A second trial evaluated the impact of gender on the effect of prophylaxis in patients who received low molecular weight heparin versus unfractionated heparin and concluded that gender did not significantly impact the antithrombotic effect of the prophylactic regimens when evaluating deep vein thrombosis (40 percent females vs. 30 percent males, $p=0.30$).⁷¹

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on deep vein thrombosis in patients who had major orthopedic surgery.^{64,83,99,106,135} In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors, the risk of deep vein thrombosis was significantly increased [RR 1.99 (1.57 to 2.51), NNH 13 to 26] (Appendix G Figure 114). A lower level of statistical heterogeneity was detected although publication bias was not detected ($I^2=42.5$ percent, Egger’s p -value=0.225). This is the same result obtained when limiting the analysis to trials published from 2001-present since all five trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, three trials remained.^{83,99,135} In patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the odds of deep vein thrombosis were significantly increased [OR 1.80 (1.38 to 2.34), NNH 21 to 34] (Appendix G Figure 115). A higher level of statistical heterogeneity was detected ($I^2=51.4$ percent). When limiting the original analysis to total knee replacement surgery, one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of deep vein thrombosis was significantly increased [RR 2.18 (1.59 to 3.01), NNH 8]. When limiting the original analysis to hip fracture surgery, one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the risk of deep vein thrombosis was significantly increased [RR 2.39 (1.75 to 3.28), NNH 9].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on deep vein thrombosis in patients who had major orthopedic surgery.⁷³ In this trial by Eriksson and colleagues in 1997, patients who had total hip replacement surgery were randomized to receive enoxaparin or desirudin prophylaxis. In patients who received injectable low molecular weight heparin agents versus

injectable or oral direct thrombin inhibitor prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 1.39 (1.15 to 1.68), NNH 15]. Subgroup analyses were not possible as this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on deep vein thrombosis in patients who had major orthopedic surgery with one trial including two separate comparisons and another trial reporting two surgical populations separately.^{75,77,80,81,85} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.66 (0.55 to 0.79), NNT 6 to 13] (Appendix G Figure 116). A higher level of statistical heterogeneity and the presence of publication bias for studies in which the risk of deep vein thrombosis was increased with low molecular weight heparin compared with vitamin K antagonists was detected ($I^2=60.9$ percent, Egger's p -value=0.033). The direction of effect was similar in all trials and four of the five trials and one of two arms in another trial found significant superiority of injectable low molecular heparins versus oral vitamin K antagonists individually. Heterogeneity, then, is due to differences in the magnitude of benefit.

When limiting the original analysis to trials published from 2001-present, one trial remained.⁷⁵ In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.57 (0.42 to 0.76), NNT 6]. When limiting the original analysis to total hip replacement surgery, three trials remained, with the one trial including two separate comparisons.^{77,80,81} In patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.61 (0.44 to 0.84), NNT 10 to 12] (Appendix G Figure 117). A higher level of statistical heterogeneity was detected ($I^2=67.6$ percent). When limiting the original analysis to total knee replacement surgery, three trials remained.^{75,80,85} In patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.71 (0.57 to 0.87), NNT 7 to 11] (Appendix G Figure 118). A higher level of statistical heterogeneity was detected ($I^2=57.2$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{98,101,102} In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.90 (0.71 to 1.14)] (Appendix G Figure 119). Statistical heterogeneity was not detected ($I^2=0$ percent) and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.¹⁰² In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly

different [RR 0.94 (0.72 to 1.21)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.^{98,101} In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.75 (0.43 to 1.30)] (Appendix G Figure 120). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin agents versus injectable or oral direct thrombin inhibitor prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{68,69} In patients who received injectable unfractionated heparin agents versus injectable or oral direct thrombin inhibitors, the risk of deep vein thrombosis was significantly increased [RR 2.31 (1.34 to 4.00) NNH 5 to 11] (Appendix G Figure 121). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery were not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.⁹⁵ In this trial by Santori and colleagues in 1994, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or venous foot pump prophylaxis. In patients who received injectable unfractionated heparin versus mechanical prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 2.63 (1.36 to 5.25) NNH 5]. Subgroup analyses were not possible as this was the only trial available.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

Three randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{56,76,90} In patients who received oral vitamin K antagonists versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.45 (0.75 to 2.82)] (Appendix G Figure 122). A higher level of statistical heterogeneity was detected ($I^2=58.5$ percent) although publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup

analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery were not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Asymptomatic Deep Vein Thrombosis

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral antiplatelet agent prophylaxis versus mechanical prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁸² This trial by Kennedy and colleagues in 2000 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus mechanical prophylaxis the odds of asymptomatic deep vein thrombosis were not significantly different [OR 1.45 (0.24 to 8.56)]. Subgroup analyses were not possible as only one trial was available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{71,96} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.70 (0.43 to 1.16)] (Appendix G Figure 123). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This result is the same when limiting the analysis to total hip replacement surgery. Subgroup analysis based on trials published 2001-present, hip fracture surgery and total knee replacement surgery were not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery, and both

contributed two separate comparisons.^{66,67} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.97 (0.85 to 1.10)] (Appendix G Figure 124). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.536). This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained and provided two separate comparisons.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 1.08 (0.69 to 1.69)] (Appendix G Figure 125). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.95 (0.83 to 1.09)] (Appendix G Figure 126). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁸⁴ This trial by Lassen and colleagues in 2007 evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.28 to 0.88), NNT 8]. Subgroup analyses were not possible as only one trial was available.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁹⁸ This trial by Stone and colleagues in 1996 evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of asymptomatic deep vein thrombosis were not significantly different [OR 1.00 (0.06 to 16.45)]. Subgroup analyses were not possible as only one trial was available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Symptomatic Deep Vein Thrombosis

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.⁸² This trial by Kennedy and colleagues in 2000 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus mechanical prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.91 (0.37 to 9.75)]. Subgroup analyses were not possible as only one trial was available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{55,71,96} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.62 (0.22 to 1.75)] (Appendix G Figure 127). Statistical heterogeneity was not detected ($I^2=0$ percent) but publication bias could not be evaluated because of too few studies. This result is the same when limiting the original analysis to total hip replacement surgery. Subgroup analysis based on trials published 2001-present, total knee replacement and hip fracture surgery were not possible because no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had major orthopedic surgery.^{74,97} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the odds of symptomatic deep vein thrombosis during the postdischarge period were not significantly different [OR 1.96 (0.20 to 19.02)] (Appendix G Figure 128). Similar results were seen when evaluating total hip replacement surgery [OR 7.54 (0.47 to 122.28)]⁹⁷ or total knee replacement surgery [OR 0.14 (0.003 to 6.90)]⁷⁴ separately.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Six randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on symptomatic deep vein thrombosis patients who had major orthopedic surgery.^{58,64,83,99,106,135} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.48 (0.21 to 1.12)] (Appendix G Figure 129). Statistical heterogeneity and the presence of publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.583). This result is the same when limiting the original analysis trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery three trials remained.^{83,99,135} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were significantly decreased [OR 0.20 (0.06 to 0.70), NNT 413 to 416] (Appendix G Figure 130). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery two trials remained.^{58,106} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.01 (0.29 to 3.49)] (Appendix G Figure 131). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.99 (0.06 to 15.83)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery, and all three provided two separate comparisons.^{66,67,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.98 (0.34 to 2.87)] (Appendix G Figure 132). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=47.5$ percent, Egger's p-value=0.476). This result is the same when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained and provided two separate comparisons.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.14 (0.02 to 1.03)] (Appendix G Figure 133). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.^{66,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 1.55 (0.58 to 4.20)] (Appendix G Figure 134). A lower level of statistical heterogeneity was detected ($I^2=35$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had total hip replacement surgery.⁷³ In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of symptomatic deep vein thrombosis during the postdischarge period were not significantly different [OR 0.51 (0.14 to 1.91)].

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Three randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{60,80,84} The trial by Hull and colleagues in 1993 provided two separate comparisons.⁸⁰ In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.87 (0.61 to 1.24)] (Appendix G Figure 135). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=28.4$ percent, Egger's p-value=0.376).

When limiting the original analysis to trials published from 2001-present one trial remained.⁸⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.00 (0.06 to 16.09)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery two trials remained.^{60,80} The trial by Colwell and colleagues in 1999 contributed two separate comparisons.⁶⁰ In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.87 (0.60 to 1.24)] (Appendix G Figure 136). A higher level of statistical heterogeneity was detected ($I^2=52.5$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{98,101} The trial by Stone and colleagues was excluded from the analysis because no events occurred in either group.⁹⁸ In remaining trial by Warwick and colleagues in 1998 patients who had total hip replacement surgery were evaluated. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 7.28 (0.14 to 367.07)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had total hip replacement surgery.⁶⁹ In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of symptomatic deep vein thrombosis during the post-discharge period were not significantly different [OR 1.50 (0.26 to 8.74)].

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Proximal Deep Vein Thrombosis

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery.⁸⁸ In this trial by Lotke and colleagues in 1996, patients who had either total hip replacement or total knee replacement surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of proximal deep vein thrombosis was not significantly

different [RR 0.78 (0.42 to 1.46)]. Subgroup analyses were not possible as this was the only trial available.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

One randomized controlled trial by Haas and colleagues in 1990 evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery.⁷⁹ In this trial, patients who had either unilateral or bilateral total knee replacement surgery were randomized to receive either aspirin or intermittent pneumatic compression prophylaxis. Results were reported separately for unilateral and bilateral surgery, however no events occurred in the unilateral surgery group therefore only the bilateral surgery group remained. In these patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.57 (0.06 to 5.77)]. Subgroup analyses were not possible as this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Nine randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on proximal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.^{55,61-63,74,86,93,96,105} In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.60 (0.38 to 0.93), NNT 14 to 50] (Appendix G Figure 137). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=37$ percent, Egger's p-value=0.450).

Subgroup analysis based on trials published from 2001-present was not possible as all trials were published prior to 2001. When limiting the original analysis to total hip replacement surgery, six trials remained, with two trials including two separate comparisons.^{55,61,63,86,93,96} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.58 (0.39 to 0.86), NNT 13 to 48] (Appendix G Figure 138). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained.^{62,74} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.32 (0.13 to 0.82), NNT 15 to 30] (Appendix G Figure 139). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was not significantly different [RR 2.25 (0.95 to 5.61)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{64,83,99,106,135} In patients who received injectable low

molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 2.19 (1.52 to 3.16), NNH 44 to 122] (Appendix G Figure 140). A higher level of statistical heterogeneity was detected but publication bias was not detected ($I^2=69.9$ percent, Egger's p -value=0.388). The direction of effect was opposing in the trials overall, with three favoring oral factor Xa inhibitors and two favoring low molecular weight heparin. Additionally, two favoring factor Xa inhibitors showed statistically significant benefit. Heterogeneity, then, is likely due to differences in the effect and magnitude of benefit. This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery, three trials remained.^{83,99,135} In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were not significantly different [OR 1.55 (0.91 to 2.66)] (Appendix G Figure 141). A high level of statistical heterogeneity was detected ($I^2=78.2$). When limiting the original analysis to total knee replacement surgery, one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 2.18 (1.04 to 4.57), NNH 45]. When limiting the original analysis to hip fracture surgery, one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 3.80 (1.92 to 7.50), NNH 38].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery with one trial including two separate comparisons.^{73,94} In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of proximal deep vein thrombosis was not significantly different [RR 0.91 (0.40 to 2.11)] (Appendix G Figure 142). A higher statistical heterogeneity was detected ($I^2=70.8$ percent) and publication bias was not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained including two separate comparisons.⁹⁴ In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of proximal deep vein thrombosis was not significantly different [RR 0.58 (0.29 to 1.17)] (Appendix G Figure 143). Statistical heterogeneity could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.⁷³ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 1.71 (1.13 to 2.59), NNH 151]. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared with enoxaparin in patients who had total hip or total knee replacement surgery.⁶⁵ Investigators reported a significant dose dependent decrease in the frequency of proximal deep vein thrombosis with increasing doses of dabigatran in both surgical groups ($p < 0.0001$) although direct comparison to enoxaparin was not made within this trial for this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Six randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.^{75,77,80,81,84,85} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.63 (0.39 to 1.00)] (Appendix G Figure 144). A higher level of statistical heterogeneity was detected but publication bias was not detected. ($I^2=55.3$ percent, Egger's p -value=0.224).

When limiting the original analysis to trials published from 2001-present, two trials remained.^{75,84} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.43 (0.05 to 4.11)] (Appendix G Figure 145). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery, three trials remained with one trial including two separate comparisons.^{77,80,81} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of proximal deep vein thrombosis were not significantly different [OR 0.67 (0.42 to 1.08)] (Appendix G Figure 146). A higher level of statistical heterogeneity was detected ($I^2=55.3$ percent). When limiting the original analysis to total knee replacement surgery, four trials remained.^{75,80,84,85} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.63 (0.30 to 1.34)] (Appendix G Figure 147). A higher level of statistical heterogeneity was detected ($I^2=68.9$ percent). Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{98,101,102} In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.65 (0.34 to 1.26)] (Appendix G Figure 148). Statistical heterogeneity was not detected ($I^2=0$ percent) and publication bias was not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.¹⁰² In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.15 (0.02 to 1.05)]. This is the same result obtained when limiting

the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.^{98,101} In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.71 (0.36 to 1.40)] (Appendix G Figure 149). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{68,69} In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 4.74 (2.99 to 7.49), NNH 11] (Appendix G Figure 150). A range for the NNH could not be calculated because the control event rate was the same in both groups. Statistical heterogeneity and publication bias were not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery could not be evaluated as no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

Three randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{56,76,90} In patients who received oral vitamin K antagonists versus mechanical prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.34 (0.16 to 0.73), NNT 11 to 31] (Appendix G Figure 151). Statistical heterogeneity was not detected ($I^2=0$ percent) and publication bias was not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery could not be evaluated as no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Distal Deep Vein Thrombosis

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on distal deep vein thrombosis in patients who had major orthopedic surgery.

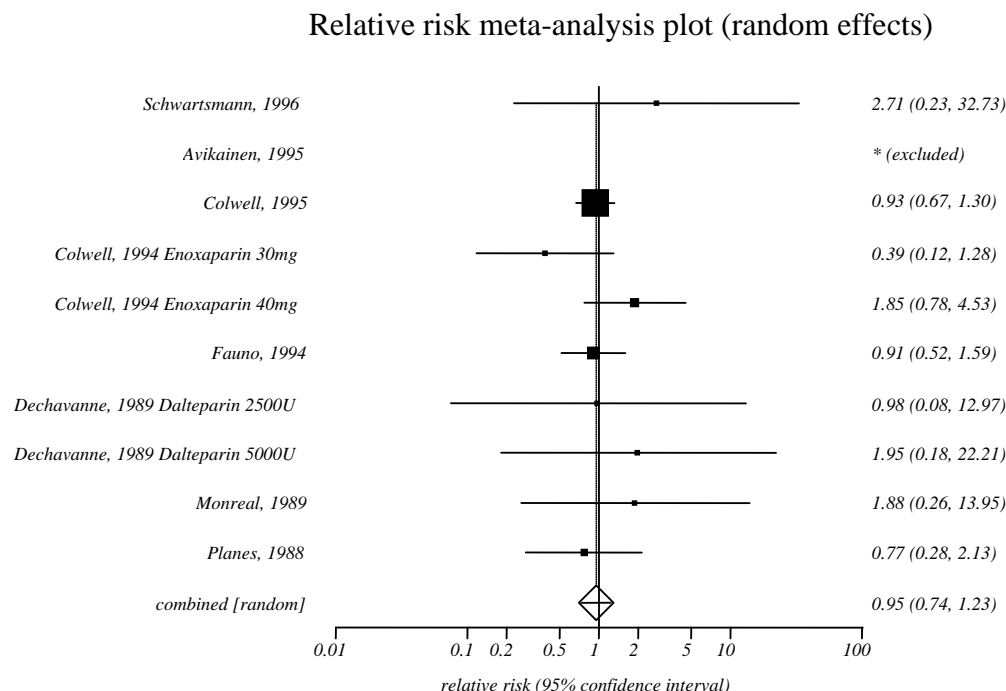
Oral Antiplatelet Agents Versus Mechanical Prophylaxis

One randomized controlled trial by Haas and colleagues in 1990 evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.⁷⁹ In this trial, patients who had total knee replacement surgery were randomized to receive either aspirin or intermittent pneumatic compression prophylaxis and results were reported separately for unilateral and bilateral surgery. In patients who received oral antiplatelet agents versus mechanical prophylaxis, the risk of distal deep vein thrombosis was significantly increased [RR 1.79 (1.15 to 2.79), NNH 4 to 6] (Appendix G Figure 152). Statistical heterogeneity and publication bias could not be evaluated because there were too few studies. Subgroup analyses were not possible as this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Eight randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on distal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.^{55,61-63,74,93,96,105} One trial was excluded from the analysis because no events occurred in the groups compared.⁵⁵ In patients who received injectable low molecular weight heparins versus injectable unfractionated heparin the risk of distal deep vein thrombosis was not significantly different [RR 0.95 (0.74 to 1.23)] (Figure 7). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.544).

Figure 7. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery



I^2 : 0 percent.

Egger's p-value: 0.544.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Subgroup analysis based on trials published from 2001-present was not possible because no trials fit this criterion. When limiting the original analysis to total hip replacement surgery, five trials remained, with two trials including two separate comparisons.^{55,61,63,93,96} One trial was excluded from the analysis because no events occurred in the groups compared.⁵⁵ In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of distal deep vein thrombosis was not significantly different [RR 1.03 (0.58 to 1.83)] (Appendix G Figure 153). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained.^{62,74} In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of distal deep vein thrombosis was not significantly different [RR 0.93 (0.69 to 1.24)] (Appendix G Figure 154). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.¹⁰⁵ In this trial, in patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the odds of distal deep vein thrombosis were not significantly different [OR 1.86 (0.19 to 18.65)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on distal deep vein thrombosis in patients who had major orthopedic surgery.^{64,83,99,106,135} In patients who received injectable low molecular weight heparins versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.02 (1.65 to 2.48), NNH 11 to 33] (Appendix G Figure 155). A lower level of statistical heterogeneity was detected ($I^2=10$ percent) and publication bias was not detected (Egger's p-value=0.106). This is the same result obtained when limiting the analysis to trials published from 2001-present since all five trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, three trials remained.^{83,99,135} In patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the odds of distal deep vein thrombosis were significantly increased [OR 1.82 (1.36 to 2.42), NNH 20 to 44] (Appendix G Figure 156). A lower level of statistical heterogeneity was found ($I^2=28.1$ percent). When limiting the original analysis to total knee replacement surgery, one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.27 (1.57 to 3.28), NNH 8]. When limiting the original analysis to hip fracture surgery, one trial remained.⁶⁴ In this trial in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.24 (1.59 to 3.17), NNH 12].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

One randomized controlled trial by Ginsberg and colleagues in 1990, including two separate comparisons, evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on distal deep vein thrombosis in patients who had major orthopedic surgery and included two separate comparisons.⁹⁴ In this trial, patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg. In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors, the risk of distal deep vein thrombosis was significantly decreased [RR 0.79 (0.67 to 0.93), NNT 16 to 18] (Appendix G Figure 157). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses were not possible as this was the only trial available.

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared with enoxaparin in patients who had total hip or total knee replacement surgery.⁶⁵ Investigators reported a significant dose dependent decrease in the frequency of distal deep vein thrombosis with increasing doses of dabigatran in both surgical groups ($p < 0.0001$) although direct comparison to enoxaparin was not made within this trial for this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on distal deep vein thrombosis in patients who had major orthopedic surgery.^{75,77} In patients who received injectable low molecular weight heparins versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.56 (0.43 to 0.73), NNT 6 to 10] (Appendix G Figure 158). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.⁷⁵ In this trial, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.60 (0.44 to 0.81), NNT 6]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.⁷⁷ In this trial, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.48 (0.30 to 0.78), NNT 9]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.^{98,101,102} One trial was excluded from the analysis because no events occurred in the groups compared.⁹⁸ In patients who received injectable low molecular weight heparins versus mechanical prophylaxis, the risk of distal deep vein thrombosis was not significantly different [RR 1.00 (0.77 to 1.29)] (Appendix G Figure 159). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.¹⁰² In this trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis, the risk of distal deep vein thrombosis was not significantly different [RR 1.01 (0.77 to 1.31)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.^{98,101} One trial was excluded from the analysis because no events occurred in the groups compared leaving one trial for the analysis.⁹⁸ In the remaining trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis, the odds of distal deep vein thrombosis were not significantly different [OR 0.84 (0.28 to 2.55)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial by Paiement and colleagues in 1987 evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.⁹⁰ In this trial, patients who had total hip replacement surgery were randomized to receive either warfarin or intermittent pneumatic compression prophylaxis. In patients who received oral vitamin K antagonists versus mechanical prophylaxis, the odds of distal deep vein thrombosis were not significantly different [OR 3.30 (0.91 to 11.91)]. Subgroup analyses were not possible as this was the only trial available.

Major Bleeding

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of oral antiplatelet agent prophylaxis versus oral vitamin K antagonist prophylaxis on major bleeding in patients who had major orthopedic surgery.¹³² This trial by Powers and colleagues in 1989 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus oral vitamin K antagonist prophylaxis the risk of major bleeding was not significantly different [RR 0.20 (0.03 to 1.23)]. Subgroup analyses were not possible as only one trial was available.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

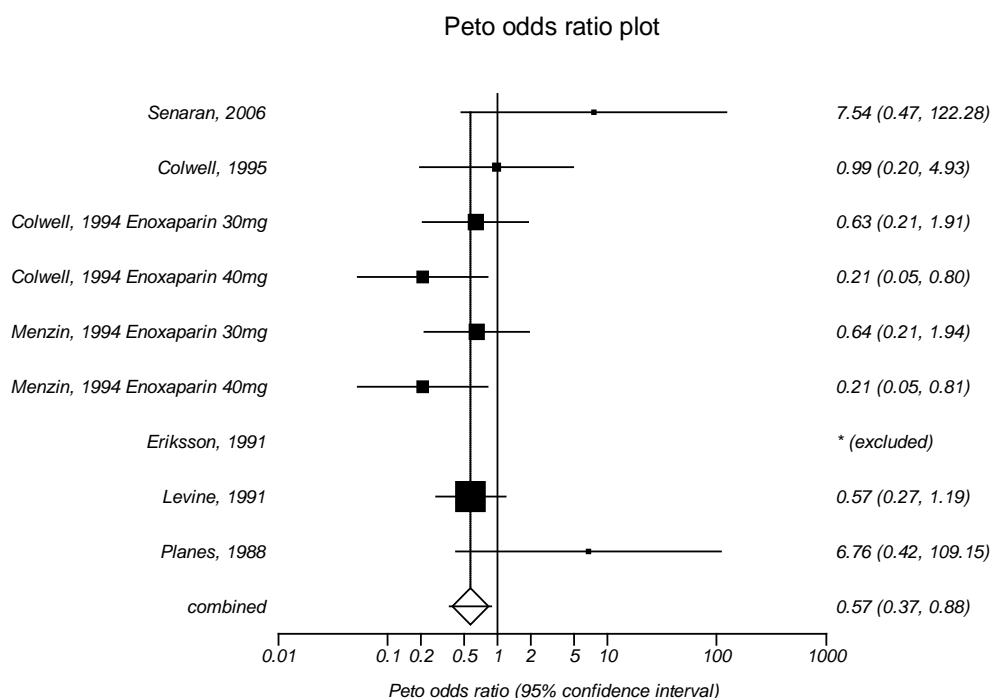
No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on major bleeding in patients who had major orthopedic surgery.^{61,62,71,86,89,93,97} Two trials provided two separate comparisons.^{61,89} The trial by Eriksson in 1991 could not be pooled as no events occurred in either group.⁷¹ In patients who received injectable low molecular weight heparin prophylaxis

versus injectable unfractionated heparin prophylaxis the odds of major bleeding were significantly decreased [OR 0.57 (0.37 to 0.88), NNT 41] (Figure 8). A range for the number needed to treat could not be calculated since the lowest control events rate was zero. A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=37.1$ percent, Egger's p -value=0.608).

Figure 8. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on major bleeding in patients undergoing major orthopedic surgery



I^2 : 37.1 percent.

Egger's p -value: 0.201.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

When limiting the original analysis to trials published from 2001-present, one trial remained.⁹⁷ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were not significantly different [OR 7.54 (0.47 to 122.28)]. When limiting the original analysis to total hip replacement surgery six trials remained.^{61,71,86,89,93,97} In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were significantly decreased [OR 0.54 (0.34 to 0.85), NNT 38] (Appendix G Figure 160). A range for the number needed to treat could not be calculated since the lowest control events rate was zero. A lower level of statistical heterogeneity was detected ($I^2=43.5$ percent). When limiting the original analysis to total knee replacement surgery one trial remained.⁶² In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were not significantly different [OR 0.99 (0.20 to 4.93)]. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on major bleeding in patients who had major orthopedic surgery.^{64,83,99,106,135} One trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment groups. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.65 (0.48 to 0.89), NNT 74 to 145] (Appendix G Figure 161). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=56.6$ percent, Egger's p -value=0.347). The direction of effect was similar in three of the four trials, with one of the trials showing statistically significant benefit of low molecular weight heparin. Heterogeneity, then, is likely due to differences in direction and the magnitude of benefit. This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery three trials remained of which one trial by Yokote and colleagues was excluded from the analysis because no events occurred in either of the treatment groups.^{83,99,135} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.64 (0.44 to 0.94), NNT 72] (Appendix G Figure 162). A range for the NNT could not be calculated since the lower bound of the control event rate was zero. Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.19 (0.06 to 0.58), NNT 62]. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were not significantly different [OR 1.04 (0.54 to 2.00)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Two controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on bleeding in patients who had major orthopedic surgery.^{147,150} Although the first study by Shorr and colleagues in 2007 did not specifically report major bleeding, the definition used in this study is similar to those used in the trials evaluated above. This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either an injectable low molecular weight heparin (enoxaparin or dalteparin) or fondaparinux prophylaxis. Bleeding was not significantly different in patients who received injectable low molecular weight heparin versus fondaparinux prophylaxis (1.5 percent versus 1.5 percent, $p=0.970$). In the second study by Gerkens and colleagues in 2010, patients who had total hip replacement, total knee replacement, or hip fracture surgery received either enoxaparin or fondaparinux. Major bleeding did not significantly differ between the two groups (1.1 percent versus 0.0 percent, respectively, $p=0.488$).

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding in patients who had major orthopedic surgery.^{66,67,73,94} The trials by Erikson and colleagues in 2007 and the trial by Ginsberg and colleagues in 2009 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.12 (0.80 to 1.57)] (Appendix G Figure 163). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.175).

When limiting the original analysis to trials published from 2001-present, three trials remained each including two separate comparisons.^{66,67,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.17 (0.79 to 1.75)] (Appendix G Figure 164). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement surgery two trials remained with the trial by Eriksson and colleagues in 2007 including two separate comparisons.^{67,73} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 0.97 (0.64 to 1.48)] (Appendix G Figure 165). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.^{66,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.46 (0.82 to 2.59)] (Appendix G Figure 166). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared with enoxaparin in patients who had total hip or total knee replacement surgery.⁶⁵ Investigators reported that major bleeding episodes were significantly higher in the dabigatran 150mg twice daily, dabigatran 225mg twice daily, and the dabigatran 300mg daily groups compared with the dabigatran 50mg twice daily group although results were not reported. When compared with enoxaparin, the dabigatran 50mg twice daily group had significantly less major bleeding episodes (0.3 percent versus 2.0 percent, p=0.047). However, the occurrence of major bleeding was not significantly different when comparing the other dabigatran groups to enoxaparin. Authors suggested a nonsignificant trend towards increased major bleeding with dabigatran 150mg twice daily, 225mg twice daily, and 300mg daily compared with enoxaparin.

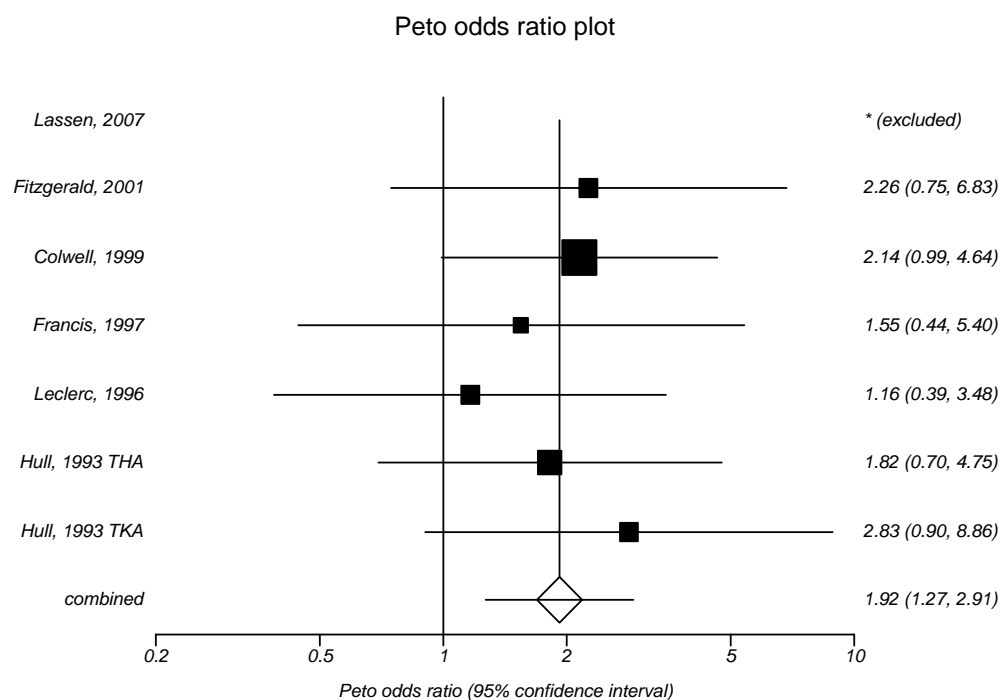
One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding during the postdischarge time period in patients who had total knee replacement surgery.⁹⁴ In this trial patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg daily. In patients who received injectable low molecular weight heparin versus injectable or oral direct

thrombin inhibitor prophylaxis the risk of major bleeding during the postdischarge period was not significantly different [RR 0.51 (0.06 to 4.58)] (Appendix G Figure 167).

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on major bleeding in patients who had major orthopedic surgery.^{60,75,77,80,81,84,85} The trial by Hull and colleagues in 1993 provided two separate comparisons and the trial by Lassen and colleagues in 2007 was excluded from the analysis because no events occurred in either group compared. Another trial by Hull and colleagues in 2000 included two separate comparisons but was not included in the pooled analysis because major bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.⁸¹ The six remaining trials were pooled, and in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of major bleeding was significantly increased [OR 1.92 (1.27 to 2.91), NNH 57 to 220] (Figure 9). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.661).

Figure 9. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major bleeding in patients undergoing major orthopedic surgery



I^2 : 0 percent.

Egger's p-value: 0.661.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

The trial by Hull and colleagues in 2000 that was excluded from the pooled analysis was evaluated separately. In this trial, patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or

warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of major bleeding was not significantly different on days 0-1 [RR 1.51 (0.92 to 2.48)] (Appendix G Figure 168) or on days 2-8 [RR 3.41 (0.77 to 15.18)] (Appendix G Figure 169).

When limiting the original pooled analysis of six trials to trials published from 2001-present two trials remained.^{75,84} The trial by Lassen and colleagues in 2007 was excluded from the analysis because no events occurred in either group.⁸⁴ In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were not significantly different [OR 2.26 (0.75 to 6.83)]. When limiting the original analysis to total hip replacement surgery three trials remained.^{60,77,80} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were significantly increased [OR 1.91 (1.11 to 3.29), NNH 58 to 220] (Appendix G Figure 170). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery four trials remained.^{75,80,84,85} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were significantly increased [OR 1.93 (1.01 to 3.67), NNH 56] (Appendix G Figure 171). A range for the number needed to harm could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected ($I^2=0$ percent). No trials evaluated patients with hip fracture surgery.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

One controlled observational study evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on bleeding in patients who had major orthopedic surgery.¹⁴⁷ Although not reported as major bleeding, the definition used in this study is similar to those used in the trials evaluated above. This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received injectable unfractionated heparin or fondaparinux prophylaxis. Bleeding was significantly increased in patients who received unfractionated heparin versus fondaparinux prophylaxis [OR 1.27 (1.06 to 1.52), NNH 253].

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on major bleeding in patients undergoing major orthopedic surgery although no events occurred therefore the risk of major bleeding could not be evaluated.⁹⁰

Major Bleeding Leading to Reoperation

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery although no events occurred therefore the risk of major bleeding leading to reoperation could not be evaluated.⁷¹

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.^{64,83,99,106} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.67 (0.28 to 1.61)] (Appendix G Figure 172). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.855). This is the same result as limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery two trials remained.^{83,99} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation was not significantly different [OR 0.72 (0.23 to 2.23)] (Appendix G Figure 173). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial remained.¹⁰⁶ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa

inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.51 (0.05 to 4.94)]. When limiting the original analysis to hip fracture surgery one trial remained.⁶⁴ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.66 (0.11 to 3.82)].

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.^{66,67,94} All three trials provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.27 (0.43 to 3.75)] (Appendix G Figure 174). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.614). This is the same result obtained when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained including two separate comparisons.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.21 (0.29 to 5.08)] (Appendix G Figure 175). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.^{66,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.36 (0.27 to 7.03)] (Appendix G Figure 176). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Two randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.^{75,77} One trial was excluded from the analysis because no events occurred in the groups compared.⁷⁵ The remaining trial by Francis and colleagues in 1997 evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.61 (0.15 to 383.70)]. Subgroup analyses were not possible as only one trial had events in the groups compared.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on major bleeding leading to reoperation in patients who had major orthopedic surgery.^{68,69} One trial was excluded from the analysis because no events occurred in the groups compared.⁶⁹ In the remaining trial by Eriksson and colleagues in 1996, patients who had total hip replacement surgery were evaluated. In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of major bleeding leading to reoperation were not significantly different [OR 0.51 (0.10 to 2.55)]. Subgroup analyses were not possible since only one trial had events in the groups compared.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery although no events occurred therefore the risk of major bleeding leading to reoperation could not be calculated.⁷⁶

Minor Bleeding

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{61,62,86,93,97} The trial by Colwell and colleagues in 1994 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of minor bleeding was not significantly different [RR 0.90 (0.63 to 1.28)] (Appendix G Figure 177). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=9.9$ percent, Egger's p-value=0.608).

When limiting the original analysis to trials published from 2001-present, one trial remained.⁹⁷ In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of minor bleeding was not significantly different [OR 0.25 (0.03 to 2.16)]. When limiting the original analysis to total hip replacement surgery, four trials remained.^{61,86,93,97} The trial by Colwell and colleagues in 1994 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of minor bleeding were not significantly different [OR 0.92 (0.57 to 1.51)] (Appendix G Figure 178). A lower level of statistical heterogeneity was detected ($I^2=31.4$ percent). When limiting the original analysis to total knee replacement surgery one trial remained.⁶² In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 0.87 (0.60 to 1.25)]. Subgroup analyses based on hip fracture surgery were not possible as no trials evaluated these surgical populations.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{64,135} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of minor bleeding were significantly decreased [OR 0.57 (0.35 to 0.94), NNT 31 to 60] (Appendix G Figure 179). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. The same results occurred when trials were limited to the years 2001-present. When limiting the original analysis to total hip replacement surgery one trial by Yokote and colleagues in 2011 remained. In this trial in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of minor bleeding were not significantly different [OR 0.85 (0.27 to 2.62)]. Subgroup analysis based on total knee replacement surgery was not possible because no trials evaluated this population. When limiting the original analysis to hip fracture surgery one trial by Eriksson and colleagues in 2001 remained. In this trial in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of minor bleeding were significantly decreased [OR 0.52 (0.30 to 0.91), NNT 54].

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{66,67,94} All three trials provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.07 (0.89 to 1.29)] (Appendix G Figure 180). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.132). This is the same result obtained when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained including two separate comparisons.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.04 (0.79 to 1.37)] (Appendix G Figure 181). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.^{66,94} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.10 (0.86 to 1.40)] (Appendix G Figure 182). Statistical heterogeneity was not detected ($I^2=0$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis on minor bleeding during the postdischarge time period in patients who had total knee replacement surgery.⁹⁴ In this trial patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg daily. In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding during the postdischarge period was not significantly different [RR 0.54 (0.15 to 1.95)] (Appendix G Figure 183).

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Eight randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{60,75,77,80,81,84,85} The trial by Hull and colleagues in 1993 provided two separate comparisons.⁸⁰ The trial Hull and colleagues in 2000 including two separate comparisons but was excluded from the pooled analysis because minor bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.⁸¹ The remaining seven trials were pooled and in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was significantly increased [RR 1.23 (1.06 to 1.43), NNH 18 to 218] (Appendix G Figure 184). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.311).

The trial by Hull and colleagues in 2000 that was excluded from the pooled analyses was evaluated separately.⁸⁰ In this trial patients who had total hip replacement surgery were

randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different on days 0-1 [RR 1.49 (0.30 to 7.37)] (Appendix G Figure 185) or on days 2-8 [RR 0.87 (0.37 to 2.06)] (Appendix G Figure 186).

When limiting the original pooled analysis of seven trials to trials published from 2001-present two trials remained.^{75,84} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.25 (0.85 to 1.83)] (Appendix G Figure 187). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery three trials remained.^{60,77,80} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.26 (0.85 to 1.86)] (Appendix G Figure 188). A lower level of statistical heterogeneity was detected ($I^2=27.8$ percent). When limiting the original analysis to total knee replacement surgery four trials remained.^{75,80,84,85} In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.17 (0.95 to 1.43)] (Appendix G Figure 189). Statistical heterogeneity was not detected ($I^2=0$ percent). No trials evaluated patients with hip fracture surgery.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on minor bleeding in patients who had major orthopedic surgery.^{76,90} In patients who received injectable low molecular weight heparin

prophylaxis versus oral vitamin K antagonist prophylaxis the odds of minor bleeding were not significantly different [OR 0.80 (0.26 to 2.41)] (Appendix G Figure 190). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to trials limited to total hip replacement surgery. Subgroup analyses based on trials published 2001-present, total knee replacement and hip fracture surgery were not possible as no trials fit these criteria.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Surgical Site Bleeding

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on surgical site bleeding in patients who had major orthopedic surgery.¹⁴⁸ This study evaluated patients who had total knee replacement surgery and who received either aspirin or warfarin prophylaxis.¹⁴⁸ The odds of surgical site bleeding for patients who received warfarin versus aspirin prophylaxis were not significantly different [AOR 0.97 (0.65 to 1.47)].

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on surgical site bleeding in patients who had major orthopedic surgery with one trial including two separate comparisons.^{61,62,97} In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of surgical site bleeding were not significantly different [OR 0.92 (0.46 to 1.82)] (Appendix G Figure 191). A lower level of statistical heterogeneity and the presence of publication bias were detected ($I^2=41.4$ percent, Egger's p-value=0.021) although the directionality of the publication bias was unclear.

When limiting the original analysis to trials published from 2001-present, one trial remained.⁹⁷ In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of surgical site bleeding was not significantly different [RR 0.75 (0.20 to 2.86)]. When limiting the original analysis to total hip replacement surgery, two trials remained with one trial including two separate comparisons.^{61,97} In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of surgical site bleeding was not significantly different [RR 0.63 (0.26 to 1.55)] (Appendix G Figure 192). A lower level of statistical heterogeneity was detected ($I^2=3.1$ percent). When limiting the original analysis to total knee replacement surgery, one trial remained.⁶² In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of surgical site bleeding were not significantly different [OR 1.78 (0.61 to 5.14)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

One randomized controlled trial by Lassen and colleagues in 2002 evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on surgical site bleeding in patients who had major orthopedic surgery.⁸³ In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin or fondaparinux prophylaxis. In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors, the odds of surgical site bleeding were not significantly different [OR 0.72 (0.45 to 1.17)]. Subgroup analyses were not possible as this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

One randomized controlled trial by Ginsberg and colleagues in 2009 evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on surgical site bleeding in patients who had major orthopedic surgery and included two separate comparisons.⁹⁴ In this trial, patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg. In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors, the risk of surgical site bleeding was significantly increased [RR 4.35 (1.51 to 12.54), NNH 100 to 105] (Appendix G Figure 193). Subgroup analyses were not possible as this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on surgical site bleeding in patients who had major orthopedic surgery.^{75,77} In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were significantly increased [OR 2.63 (1.31 to 5.28), NNH 23 to 64] (Appendix G Figure 194). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.⁷⁵ In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were not significantly different [OR 2.05 (0.80 to 5.29)]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.⁷⁷ In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were significantly increased [OR 3.53 (1.27 to 9.84), NNH 42]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on major surgical site bleeding in patients who

had major orthopedic surgery.^{60,80,81} The trial by Hull and colleagues in 2000 was excluded from the pooled analysis because major surgical site bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.⁸¹ The remaining two trials were pooled and in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of major surgical site bleeding were significantly increased [OR 2.51 (1.38 to 4.54), NNH 70 to 224] (Appendix G Figure 195). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

The trial by Hull and colleagues in 2000 that was excluded from the pooled analysis was evaluated separately.⁸¹ In this trial patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of major surgical site bleeding was significantly increased on days 0 to 1 [RR 1.72 (1.02 to 2.92), NNH 47] (Appendix G Figure 196) but was not significantly different on days 2 to 8 [RR 2.72 (0.59 to 12.44)] (Appendix G Figure 197). A range for the number needed to harm for major surgical site bleeding on days 0-1 could not be calculated because the control events rate was the same in both groups.

When limiting the original pooled analysis of two trials to total hip replacement surgery, one trial remained.⁶⁰ In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of major surgical site bleeding were significantly increased [OR 2.56 (1.04 to 6.30), NNH 216]. Subgroup analyses based on trials published from 2001-present, total knee replacement or hip fracture surgery were not possible because no trials fit these criteria. The trial by Hull and colleagues in 1993 evaluated both total hip and knee replacement surgery although did not report results separately. Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on minor surgical site bleeding in patients who had major orthopedic surgery.^{60,80,81} The trial by Hull and colleagues in 2000 was excluded from the pooled analysis because minor surgical site bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.⁸¹ The two remaining trials were pooled and in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of minor surgical site bleeding were not significantly different [OR 1.34 (0.91 to 1.97)] (Appendix G Figure 198). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

The trial by Hull and colleagues in 2000 was excluded from the pooled analysis and was evaluated separately.⁸¹ In this trial patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. No events occurred in the comparison of dalteparin initiated preoperatively versus warfarin. In the remaining comparison, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of minor surgical site bleeding were not significantly different on days 0 to 1 [OR 7.42 (0.15 to 373.92)] or on days two to eight [OR 7.43 (0.46 to 119.03)].

When limiting the original pooled analysis of two trials to total hip replacement surgery, one trial remained.⁶⁰ In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of minor surgical site bleeding were not significantly different [OR 1.37 (0.93 to 2.02)]. Subgroup analyses based on trials published

from 2001-present, total knee replacement or hip fracture surgery were not possible because no trials fit these criteria. Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

One randomized controlled trial by Eriksson and colleagues in 1996 evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on surgical site bleeding in patients who had major orthopedic surgery.⁶⁸ In this trial, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or desirudin. In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors, the odds of surgical site bleeding were not significantly different [OR 0.87 (0.31 to 2.43)]. Subgroup analyses were not possible as this was the only trial available.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Infection

No randomized controlled trials or controlled observational studies compared between pharmacological and/or mechanical classes of prophylaxis to evaluate this outcome.

Bleeding Leading to Transfusion

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

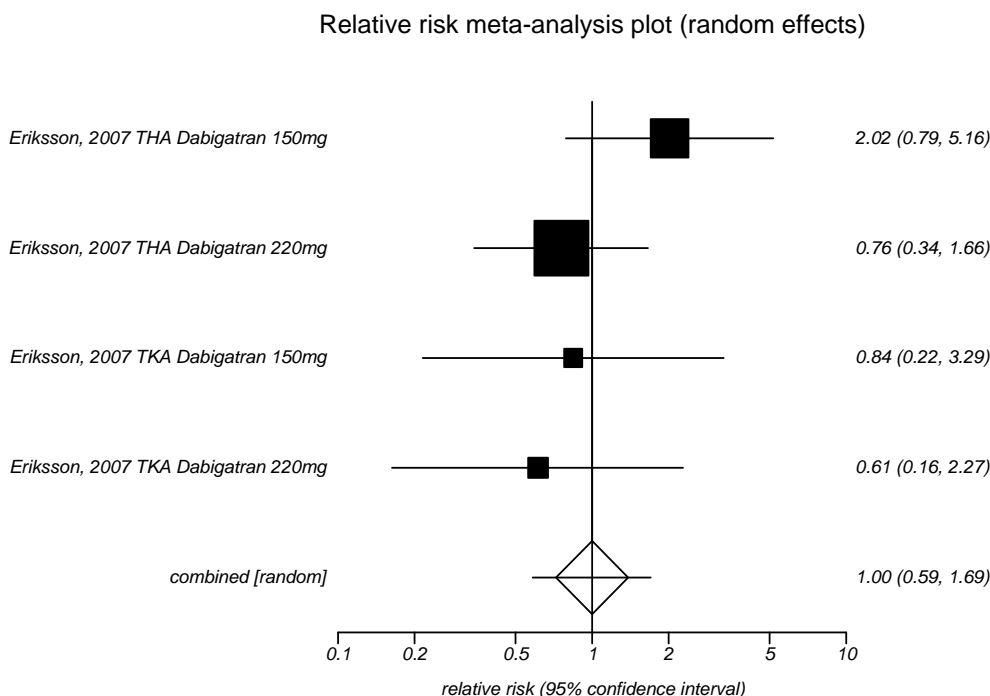
No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery and each trial included two separate comparisons.^{66,67} In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not significantly different [RR 1.00 (0.59 to 1.69)] (Figure 10). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p-value=0.827). This is the same result obtained when limiting the original analysis to trials published from 2001-present. When limiting the original analysis to total hip replacement surgery, one trial which included two separate comparisons remained.⁶⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not significantly different [RR 1.19 (0.46 to 3.10)] (Appendix G Figure 199). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial which included two separate comparisons remained.⁶⁶ In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not statistically significant [RR 0.71 (0.26 to 1.98)] (Appendix G Figure 200). Statistical heterogeneity could not be evaluated because of too few studies. No trials evaluated patients who had hip fracture surgery.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Figure 10. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery (same as analysis of 2001-present)



I²: 0 percent.

Egger's p-value: P=0.823.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.⁷⁷ This trial by Francis and colleagues in 1997, evaluated patients who had total hip replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of bleeding leading to transfusion were not significantly different [OR 1.71 (0.42 to 6.90)]. Subgroup analyses were not possible because only one trial was available.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on bleeding leading to transfusion in patients who had major orthopedic surgery.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion although no events occurred in the groups compared therefore the risk could not be calculated.⁷⁶

Heparin Induced Thrombocytopenia

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on heparin-induced thrombocytopenia in patients who had major orthopedic surgery.^{61,86,97} One trial by Colwell and colleagues included two separate comparisons.⁶¹ One trial was excluded from the analysis because no events occurred in the groups compared.⁹⁷ In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the odds of heparin induced thrombocytopenia was significantly decreased [OR 0.12 (0.03 to 0.43), NNT 34 to 202] (Appendix G Figure 201). Statistical heterogeneity was not detected ($I^2=0$ percent) and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the original analysis to total hip replacement as all three trials were conducted in this surgical population. No trials evaluated total knee replacement or hip fracture surgery. When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared.⁹⁷

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on heparin-induced thrombocytopenia in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of heparin-induced thrombocytopenia could not be calculated.⁶⁰

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Discomfort

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

No randomized controlled trial or controlled observational studies evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

One randomized controlled trial by Warwick and colleagues in 1998 evaluated the impact of injectable low molecular weight heparin versus mechanical prophylaxis on discomfort in patients who had major orthopedic surgery.¹⁰¹ In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin or venous foot pump prophylaxis. Discomfort reported as “quite a bit of difficulty sleeping” or “quite uncomfortable” in patients who received mechanical prophylaxis and “quite painful” or “quite uncomfortable” in patients who received low molecular weight heparin was used. Although the discomfort was defined differently in each arm, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis the risk of discomfort was significantly decreased [RR 0.49 (0.29 to 0.82), NNT 7].

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Readmission

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on readmission in patients who had major orthopedic surgery.^{61,97} One trial by Colwell and colleagues included two separate comparisons.⁶¹ In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the risk of readmission was not significantly different [RR 0.82 (0.20 to 3.38)] (Appendix G Figure 202). A lower level of statistical heterogeneity was detected ($I^2=14.1$ percent) and publication bias could not be evaluated because of too few studies. The reasons reported for readmission in the low molecular weight heparin group included deep vein thrombosis while in the unfractionated heparin group included deep vein thrombosis and pulmonary embolism. This is the same results obtained when limiting the original analysis to total hip replacement as both trials were conducted in this surgical population. No trials evaluated total knee replacement or hip fracture surgery. When

limiting the original analysis to trials published from 2001-present, one trial remained.⁹⁷ In this trial, in patients who received injectable low molecular weight heparin versus injectable unfractionated heparin prophylaxis, the odds of readmission were not significantly different [OR 7.54 (0.47 to 122.23)]. The reported reason for readmission in the low molecular weight heparin group was venous thromboembolic disease, while no readmissions occurred in the unfractionated heparin group.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on readmission in patients who had major orthopedic surgery.^{101,102} In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of readmission were not significantly different [OR 0.83 (0.22 to 3.11)] (Appendix G Figure 203). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present one trial by Warwick and colleagues remained.¹⁰² In this trial in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of readmission were not significantly different [OR 0.78 (0.17 to 3.50)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement, one trial remained.¹⁰¹ In this trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis the odds of readmission were not significantly different [OR 1.03 (0.06 to 16.52)]. No trials evaluated hip fracture surgery.

Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

One randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on readmission in patients who had major orthopedic surgery.⁵⁶ This trial evaluated patients who had total hip replacement surgery. In patients who received oral vitamin K antagonist prophylaxis versus mechanical prophylaxis, the odds of readmission were not significantly different [OR 0.15 (0.003 to 7.58)]. Subgroup analyses were not possible because only one trial was available.

Reoperation

Oral Antiplatelet Agents Versus Oral Vitamin K Antagonists

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Antiplatelet Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable Unfractionated Heparin

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Factor Xa Inhibitors

One randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on reoperation in patients who had major orthopedic surgery.⁵⁸ This trial by Bonneaux and colleagues in 2006

evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the risk of reoperation was not significantly different [RR 0.25 (0.04 to 1.63)]. Subgroup analyses were not possible since this was the only trial available.

Injectable Low Molecular Weight Heparin Agents Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Low Molecular Weight Heparin Agents Versus Oral Vitamin K Antagonists

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on reoperation in patients who had major orthopedic surgery.^{75,77} One trial was excluded from the analysis because no events occurred, leaving the trial by Francis and colleagues in 1997.⁷⁷ This trial evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of reoperation was not significantly different [RR 0.85 (0.59 to 1.22)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable Low Molecular Weight Heparin Agents Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Direct Thrombin Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Injectable or Oral Factor Xa Inhibitors

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable Unfractionated Heparin Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral Vitamin K Antagonists Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Strength of Evidence and Applicability of the Body of Evidence

Key Question 5 compared between pharmacologic and mechanical device classes. Compared with injectable unfractionated heparin, there was a high strength of evidence that low molecular weight heparin decreased the risk of proximal deep vein thrombosis and the odds of major bleeding although did not impact the risk of distal deep vein thrombosis. There was moderate strength of evidence that low molecular weight heparin agents decreased the odds of pulmonary embolism, heparin induced thrombocytopenia and the risk of deep vein thrombosis, although did not impact the risk of mortality or minor bleeding. There was low strength of evidence that there was no difference in the risk of nonfatal pulmonary embolism, asymptomatic or symptomatic deep vein thrombosis, surgical site bleeding or readmission. Compared with factor Xa inhibitors, there was high strength of evidence that low molecular weight heparins increased the risk of distal deep vein thrombosis and moderate strength of evidence that low molecular weight heparins increased the risk of deep vein thrombosis and the odds of major bleeding. There was moderate strength of evidence that there was no difference in the odds of nonfatal pulmonary embolism, mortality, symptomatic deep vein thrombosis, or major bleeding leading to reoperation. There was low strength of evidence that there was no difference in the odds of symptomatic objectively confirmed venous thromboembolism or fatal pulmonary embolism and that there was an increased odds of proximal deep vein thrombosis and decreased odds of minor bleeding. All other outcomes were rated as insufficient evidence. Compared with vitamin K antagonists, there was high strength of evidence that low molecular weight heparins increased the odds of major bleeding and moderate strength of evidence they increased the odds of minor bleeding and low strength of evidence they increased the odds of surgical site bleeding. Strength of evidence was moderate that low molecular weight heparins decreased the risk of distal deep vein thrombosis and low that they decreased the risk of deep vein thrombosis compared with vitamin K antagonists. Strength of evidence was moderate that there was no difference in the odds of pulmonary embolism, mortality and symptomatic deep vein thrombosis and low that there was no difference in the risk of proximal deep vein thrombosis or the odds of symptomatic objectively confirmed venous thromboembolism or nonfatal pulmonary embolism. All other outcomes were rated as insufficient.

For both the comparisons of low molecular weight heparin with direct thrombin inhibitors and with mechanical prophylaxis, there were no significant differences between the two classes. Compared with injectable or oral direct thrombin inhibitors, there was high strength of evidence that there was no difference with the use of injectable low molecular weight heparin agents in the risk of bleeding leading to transfusion and there was moderate strength of evidence that there was no difference in the risk of major venous thromboembolism, pulmonary embolism, mortality, asymptomatic or symptomatic deep vein thrombosis, major bleeding, major bleeding leading to reoperation or minor bleeding. The strength of evidence was low that there was no difference in the odds of fatal or nonfatal pulmonary embolism or the risk of proximal deep vein thrombosis. Other outcomes were rated as insufficient. For the comparison of injectable low molecular weight heparin to mechanical prophylaxis, few studies were available and most outcomes were rated as insufficient. There was moderate strength of evidence that there was no significant difference in the risk of deep vein thrombosis, proximal or distal deep vein thrombosis and there was low strength of evidence that there was no difference in the odds of mortality and readmission.

For other class comparisons, there were relatively less data and more outcomes were rated with insufficient evidence. Compared with oral or injectable direct thrombin inhibitors, there was

moderate strength of evidence that injectable unfractionated heparin increased the risk of deep vein thrombosis and the odds of proximal deep vein thrombosis while there was low strength of evidence that there was no difference in the risk of pulmonary embolism, fatal pulmonary embolism, mortality, or major bleeding leading to reoperation. Compared with mechanical prophylaxis, there was moderate strength of evidence that oral vitamin K antagonists decreased the risk of proximal deep vein thrombosis with a low strength of evidence that there was no difference in the risk of deep vein thrombosis or minor bleeding. Compared with mechanical prophylaxis there was moderate strength of evidence that oral antiplatelet prophylaxis increased the risk of deep vein thrombosis. All other outcomes were rated as insufficient for this comparison. All outcomes were rated as insufficient for the following comparisons: oral antiplatelet versus oral vitamin K antagonists, injectable unfractionated heparin versus factor Xa inhibitors, and injectable unfractionated heparin versus mechanical prophylaxis.

Overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data.

Table 11. Significant differences between comparative groups for outcomes in base case and subgroup analyses in Key Question 5

		ATP vs. VKA	ATP vs. Mech	LMWH vs. UFH	LMWH vs. FXA	LMWH vs. DTI	LMWH vs. VKA	LMWH vs. Mech	UFH vs. DTI	UFH vs. FXA	UFH vs. Mech	VKA vs. Mech
Final health outcomes	Base Case	↑ Death* ↑ fPE*		↓ PE	↑ Death*					↑ Death*		
	2001-Present	↑ Death* ↑ fPE*			↑ Death*					↑ Death*		
	THR			↓ PE ↓ nfPE	↓ sVTE ↓ nfPE							
	TKR											
	HFS			↑ PE ↑ nfPE								
Intermediate health outcomes	Base Case		↑ DVT ↑ dDVT	↓ DVT ↓ pDVT	↑ DVT ↑ pDVT ↑ dDVT	↑ DVT ↓ dDVT	↓ DVT ↓ asDVT ↓ pDVT ↓ dDVT		↑ DVT ↑ p DVT		↑ DVT	↓ pDVT
	2001-Present				↑ DVT ↑ pDVT ↑ dDVT	↓ dDVT	↓ DVT ↓ asDVT ↓ dDVT					
	THR			↓ DVT ↓ pDVT	↑ DVT ↑ dDVT ↓ sDVT	↑ pDVT	↓ DVT ↓ dDVT		↑ DVT ↑ pDVT			↓ pDVT
	TKR		↑ DVT ↑ dDVT	↓ DVT ↓ pDVT	↑ DVT ↑ pDVT ↑ dDVT	↓ dDVT	↓ DVT ↓ asDVT ↓ dDVT					
	HFS			↑ DVT	↑ DVT ↑ pDVT ↑ dDVT							

Table 11. Significant differences between comparative groups for outcomes in base case and subgroup analyses in Key Question 5 (continued)

		ATP vs. VKA	ATP vs. Mech	LMWH vs. UFH	LMWH vs. FXA	LMWH vs. DTI	LMWH vs. VKA	LMWH vs. Mech	UFH vs. DTI	UFH vs. FXA	UFH vs. Mech	VKA vs. Mech
Adverse outcomes	Base Case			↓ MJB ↓ HIT	↓ MJB ↓ MNB	↑ SSB	↑ MJB ↑ MNB ↑ SSB	↓ DC		↑ MJB*		
	2001-Present				↓ MJB ↓ MNB	↑ SSB				↑ MJB*		
	THR			↓ MJB ↓ HIT	↓ MJB		↑ MJB ↑ SSB	↓ DC				
	TKR				↓ MJB	↑ SSB	↑ MJB					
	HFS				↓ MNB							

asDVT = asymptomatic deep vein thrombosis; ATP = antiplatelet; DC = discomfort; dDVT = distal deep vein thrombosis; DTI = direct thrombin inhibitor; DVT = deep venous thrombosis ; fPE = fatal pulmonary embolism; FXA = factor Xa inhibitors; HFS = hip fracture surgery; HIT = heparin induced thrombocytopenia; LMWH = low molecular weight heparin; Mech = mechanical prophylaxis; MJB = major bleeding; MNB = minor bleeding; nf PE = nonfatal pulmonary embolism; OBS = data derived from a controlled observational study; pDVT = proximal deep vein thrombosis; PE = pulmonary embolism; sDVT = symptomatic deep vein thrombosis; SSB = surgical site bleeding; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKA = vitamin K antagonist; vs = versus

*Based on observational data.

↓ Denotes significantly fewer occurrences in group A vs. group B.

↑ Denotes significantly more occurrences in group A than group B.

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?*

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Symptomatic objectively confirmed VTE	Antiplatelet versus oral VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	1 RCT	No	OR 0.13 (0.01 to 2.15)	NA
		1 RCT	No	One RCT evaluated this outcome during the postdischarge period and showed an OR 7.54 (0.47 to 122.28)	NA
	LMWH versus factor Xa inhibitors	5 RCTs	Yes	OR 0.70 (0.48 to 1.02)	38.5
	• Limited to 2001-present	5 RCTs	Yes	OR 0.70 (0.48 to 1.02)	38.5
	• Limited to THR	3 RCTs	Yes	OR 0.53 (0.32 to 0.87)†	0
	• Limited to TKR	1 RCT	No	OR 1.97 (0.71 to 5.45)	NA
	• Limited to HFS	1 RCT	No	OR 0.75 (0.37 to 1.55)	NA
	LMWH versus DTI	0	---	---	---
	LMWH versus VKA	2 RCTs	Yes	OR 1.00 (0.69 to 1.46)	NA
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed an OR 2.24 (0.65 to 7.79)	NA
	• Limited to THR	1 RCT	No	OR 0.97 (0.66 to 1.41)	NA
	• Limited to TKR	1 RCT	No	OR 2.71 (0.38 to 19.35)	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---
Major venous thromboembolism	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	0	---	---	---
	LMWH versus factor Xa inhibitors	0	---	---	---
	LMWH versus DTI	3 RCTs	Yes	RR 1.26 (0.98 to 1.62)	0
	• Limited to 2001-present	2 RCTs	Yes	RR 1.08 (0.78 to 1.50)	0
	• Limited to THR	2 RCTs	Yes	RR 1.28 (0.94 to 1.76)	18.6
	• Limited to TKR	1 RCT	No	RR 1.11 (0.63 to 1.96)	NA
	LMWH versus VKA	0	---	---	---
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Pulmonary embolism	Antiplatelet versus VKA	1 RCT	No	OR 7.28 (0.14 to 366.83)	NA
	Antiplatelet versus mechanical	1 RCT	No	OR 7.09 (0.14 to 357.70)	NA
	LMWH versus UFH	10 RCTs	Yes	OR 0.48 (0.24 to 0.95)†	59.7
		1 RCT	No	1 trial evaluated this outcome at the postdischarge period and showed a RR 0.13 (0.01 to 1.17)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	7 RCTs	Yes	OR 0.28 (0.13 to 0.62)†	0
	• Limited to TKR	2 RCTs	No	1 trial had no events in the groups compared, the remaining trial showed OR 0.13 (0.01 to 2.13)	NA
	• Limited to HFS	1 RCT	No	OR 7.95 (1.53 to 41.29)†	NA
	LMWH versus factor Xa inhibitor	2 RCTs	No	1 trial had no events in the groups compared, the remaining trial showed OR 3.34 (0.58 to 19.32)	NA
	• Limited to 2001-present	2 RCTs	No	1 trial had no events in the groups compared, the remaining trial showed OR 3.34 (0.58 to 19.32)	NA
	• Limited to THR	1 RCT	No	1 trial had no events in the groups compared	NA
	• Limited to TKR	1 RCT	No	OR 3.34 (0.58 to 19.32)	NA
	LMWH versus DTI	3 RCTs	Yes	RR 1.18 (0.41 to 3.39)	0
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed an OR 3.89 (0.78 to 19.34)	NA
	• Limited to 2001-present	2 RCTs	Yes	RR 1.25 (0.35 to 4.39)	0
	• Limited to THR	2 RCTs	Yes	RR 1.03 (0.32 to 3.36)	0
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 2.00 (0.18 to 22.02)	NA
	LMWH versus VKA	5 RCTs	Yes	OR 1.11 (0.57 to 2.19)	28.7
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed an OR 1.01 (0.06 to 16.14)	NA
	• Limited to 2001-present	2 RCTs	Yes	OR 1.96 (0.20 to 18.94)	NA
	• Limited to THR	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 1.23 (0.58 to 2.63)	NA
	• Limited to TKR	3 RCTs	Yes	OR 0.75 (0.17 to 3.31)	48.2
	LMWH versus mechanical	1 RCT	No	OR 0.13 (0.003 to 6.72)	NA
	UFH versus DTI	2 RCTs	Yes	OR 3.23 (0.56 to 18.98)	NA
	• Limited to THR	2 RCTs	Yes	OR 3.23 (0.56 to 18.98)	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Fatal pulmonary embolism	Antiplatelet versus VKA	1 RCT, 1 OBS	No	RCT: OR 7.28 (0.14 to 366.83); observational data suggested a significantly higher percent of patients who received aspirin had a fatal pulmonary embolism than those who received warfarin	NA
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	10 RCTs	No	Nine trials had no events; the remaining trial showed OR 0.13 (0.003 to 6.73)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	7 RCTs	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	OR 0.13 (0.003 to 6.73)	NA
	• Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
	LMWH versus factor Xa inhibitor	5 RCTs	Yes	One trial had no events in the groups compared, the remaining trials showed OR 0.90 (0.38 to 2.13)	0
	• Limited to 2001-present	5 RCTs	Yes	One trial had no events in the groups compared, the remaining trials showed OR 0.90 (0.38 to 2.13)	0
	• Limited to THR	3 RCTs	Yes	One trial had no events in the groups compared, the remaining trial showed OR 1.00 (0.14 to 7.10)	NA
	• Limited to TKR	1 RCT	No	OR 1.00 (0.06 to 16.01)	NA
	• Limited to HFS	1 RCT	No	OR 0.86 (0.31 to 2.39)	NA
	LMWH versus DTI	2 RCTs	Yes	OR 1.43 (0.08 to 24.82)	31.7
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed an OR 0.14 (0.003 to 6.97)	NA
	• Limited to 2001-present	2 RCTs	Yes	OR 1.43 (0.08 to 24.82)	31.7
	• Limited to THR	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 0.14 (0.003 to 6.91)	NA
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 4.00 (0.36 to 44.03)	NA
	LMWH versus VKA	4 RCTs	No	Three trials had no events and 1 trial showed OR 7.29 (0.14 to 367.30)	NA
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period although no events occurred	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	One trials had no events; the remaining trial showed OR 7.29 (0.14 to 367.30)	NA
	• Limited to TKR	2 RCTs	No	No events occurred in the groups compared	NA
	LMWH versus mechanical	2 RCTs	Yes	One trial had no events; the remaining trial showed OR 0.14 (0.01 to 2.25)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Fatal pulmonary embolism (continued)	• Limited to 2001-present	1 RCT	No	OR 0.14 (0.01 to 2.25)	NA
	• Limited to THR	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	OR 0.14 (0.01 to 2.25)	NA
	UFH versus DTI	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
Nonfatal pulmonary embolism	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
	Antiplatelet versus VKA	1 RCT, 1 OBS	No	RCT: No events occurred in the groups compared; observational data suggest no significant difference	NA
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	10 RCTs	Yes	OR 0.50 (0.25 to 1.00)	58.8
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed a RR 0.13 (0.01 to 1.17)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	7 RCTs	Yes	OR 0.28 (0.13 to 0.62)†	0
	• Limited to TKR	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.13 (0.003 to 6.73)	NA
	• Limited to HFS	1 RCT	No	OR 7.95 (1.53 to 41.29)	NA
	LMWH versus factor Xa inhibitor	5 RCTs	Yes	One trial had no events in the groups compared; the remaining trials showed OR 0.68 (0.34 to 1.37)	49.5
	• Limited to 2001-present	5 RCTs	Yes	One trial had no events in the groups compared; the remaining trials showed OR 0.68 (0.34 to 1.37)	49.5
	• Limited to THR	3 RCTs	Yes	One trial had no events in the groups compared; the remaining trials showed OR 0.39 (0.16 to 0.95)†	NA
	• Limited to TKR	1 RCT	No	OR 1.95 (0.39 to 9.72)	NA
	• Limited to HFS	1 RCT	No	OR 1.32 (0.30 to 5.81)	NA
	LMWH versus DTI	2 RCTs	Yes	OR 0.93 (0.23 to 3.66)	53.7
	• Limited to 2001-present	2 RCTs	Yes	OR 0.93 (0.23 to 3.66)	53.7
	• Limited to THR	1 RCT (2 comp)	Yes	RR 1.61 (0.13 to 19.37)	NA
	• Limited to TKR	1 RCT (2 comp)	No	One arm had no events; the remaining arm showed OR 0.14 (0.003 to 6.93)	NA
	LMWH versus VKA	3 RCTs	Yes	OR 1.00 (0.20 to 4.95)	NA
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed an OR 1.01 (0.06 to 16.14)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Nonfatal pulmonary embolism (continued)	• Limited to 2001-present	1 RCT	No	OR 7.46 (0.46 to 120.00)	NA
	• Limited to THR	1 RCT (2 comp)	No	No events occurred in the groups compared	NA
	• Limited to TKR	2 RCTs	Yes	OR 1.00 (0.20 to 4.95)	NA
	LMWH versus mechanical	1 RCT	No	OR 0.13 (0.003 to 6.72)	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus DTI	2 RCTs	Yes	OR 3.27 (0.56 to 18.98)	NA
	• Limited to THR	2 RCTs	Yes	OR 3.27 (0.56 to 18.98)	NA
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Post thrombotic Syndrome		0	---	---	---
Mortality	Antiplatelet versus VKA	1 RCT, 2 OBS	No	RR 0.98 (0.32 to 3.05); observational data conflict with one study suggesting no significant difference and a second suggesting significantly higher percent of deaths in patients who received aspirin versus warfarin	NA
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	8 RCTs	Yes	OR 0.39 (0.10 to 1.49)	0
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	7 RCTs	Yes	OR 0.21 (0.03 to 1.59)	0
	• Limited to HFS	1 RCT	No	RR 0.64 (0.13 to 3.06)	NA
	LMWH versus factor Xa inhibitor	5 RCTs 2 OBS	Yes (RCTs)	One trial had no events in the groups compared, the remaining trials showed OR 1.08 (0.72 to 1.60); one observational study suggests significantly higher percent of deaths in patients who received LMWH versus factor Xa inhibitors while the other study suggests no difference	0
	• Limited to 2001-present	5 RCTs 1 OBS	Yes (RCT)	One trial had no events in the groups compared, the remaining trials showed OR 1.08 (0.72 to 1.60); Observational study is supportive	0
	• Limited to THR	3 RCTs	Yes	One trial had no events in the groups compared, the remaining trials showed OR 0.88 (0.32 to 2.42)	NA
	• Limited to TKR	1 RCT	No	OR 1.49 (0.26 to 8.65)	NA
	• Limited to HFS	1 RCT	No	OR 1.10 (0.70 to 1.72)	NA
	LMWH versus DTI	4 RCTs	Yes	RR 0.45 (0.15 to 1.36)	0
	• Limited to 2001-present	3 RCTs	Yes	RR 0.54 (0.15 to 1.98)	0

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Mortality (continued)	• Limited to THR	2 RCTs	Yes	RR 0.27 (0.06 to 1.23)	0
	• Limited to TKR	2 RCTs	Yes	RR 0.80 (0.16 to 4.17)	0
	LMWH versus VKA	6 RCTs	Yes	OR 0.79 (0.42 to 1.50)	0
	• Limited to 2001-present	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.37 (0.05 to 2.66)	NA
	• Limited to THR	2 RCTs	Yes	RR 0.81 (0.36 to 1.82)	0
	• Limited to TKR	3 RCTs	Yes	OR 0.52 (0.10 to 2.57)	NA
	LMWH versus mechanical	2 RCTs	Yes	OR 0.31 (0.05 to 1.80)	NA
	• Limited to 2001-present	1 RCT	No	OR 0.38 (0.05 to 2.73)	NA
	• Limited to THR	1 RCT	No	OR 0.14 (0.003 to 7.01)	NA
	• Limited to TKR	1 RCT	No	OR 0.38 (0.05 to 2.73)	NA
	UFH versus DTI	2 RCTs	Yes	OR 7.13 (0.74 to 68.80)	NA
	• Limited to THR	2 RCTs	Yes	OR 7.13 (0.74 to 68.80)	NA
	UFH versus factor Xa inhibitor	1 OBS	No	Observational data suggested significantly higher percent of deaths in patients who received UFH versus factor Xa inhibitor	NA
	UFH versus mechanical	1 RCT	No	OR 7.62 (0.15 to 384.19)	NA
	VKA versus mechanical	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.95 (0.06 to 15.33)	NA
	• Limited to THR	1 RCT	No	OR 0.95 (0.06 to 15.33)	NA
Mortality due to bleeding	Antiplatelet versus VKA	1 RCT	No	No events occurred in the groups compared	NA
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	7 RCTs	No	Six trials had no events in the groups compared, the remaining trial showed OR 0.13 (0.003 to 6.52)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	6 RCTs	No	No events occurred in the groups compared	NA
	• Limited to HFS	1 RCT	No	OR 0.13 (0.003 to 6.52)	NA
	LMWH versus factor Xa inhibitor	5 RCTs 1 OBS	No	Four trials had no events in the groups compared, the remaining trial showed OR 7.29 (0.14 to 367.58); Observational data suggest no difference	NA
	• Limited to 2001-present	2 RCTs 1 OBS	No	One trial had no events in the groups compared, the remaining trial showed OR 7.29 (0.14 to 367.58); Observational data suggest no difference	NA
	• Limited to THR	3 RCTs	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to HFS	1 RCT	No	OR 7.29 (0.14 to 367.58)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Mortality due to bleeding (continued)	LMWH versus DTI	3 RCTs	Yes	Two trials had no events in the groups compared, the remaining trial included two comparisons pooled to show RR 0.67 (0.07 to 6.40)	NA
	• Limited to 2001-present	3 RCTs	Yes	Two trials had no events in the groups compared, the remaining trial included two comparisons pooled to show RR 0.67 (0.07 to 6.40)	NA
	• Limited to THR	1 RCT (2 comp)	Yes	RR 0.67 (0.07 to 6.40)	NA
	• Limited to TKR	2 RCTs	No	No events occurred in the groups compared	NA
	LMWH versus VKA	4 RCTs	No	Three trials had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 6.94)	NA
	• Limited to 2001-present	1 RCT	No	OR 0.14 (0.003 to 6.94)	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to TKR	3 RCTs	No	Two trials had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 6.94)	NA
	LMWH versus mechanical	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 7.01)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	1 RCT	No	OR 0.14 (0.003 to 7.01)	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
	UFH versus DTI	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
	VKA versus mechanical	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
Health related quality of life		0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Deep vein thrombosis	Antiplatelet versus VKA	1 RCT	No	RR 1.06 (0.87 to 1.30)	NA
	• Gender	1 RCT	No	No significant difference	NA
	Antiplatelet versus mechanical	2 RCTs	Yes	RR 1.63 (1.11 to 2.39)†	0
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 1.63 (1.08 to 2.44)†	NA
	• Limited to HFS	1 RCT	No	RR 1.68 (0.55 to 5.19)	NA
	LMWH versus UFH	13 RCTs	Yes	RR 0.80 (0.65 to 0.99)†	34.3
		1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17)	NA
	• Limited to 2001-present	1 RCT	No	OR 0.13 (0.01 to 2.15)	NA
	• Limited to THR	10 RCTs	Yes	RR 0.75 (0.58 to 0.97)†	26.4
		1 RCT	No	1 trial ineligible for pooling showed RR 1.60 (0.21 to 12.06)	NA
	• Limited to TKR	2 RCTs	Yes	RR 0.75 (0.58 to 0.96)†	NA
		1 RCT	No	1 trial ineligible for pooling showed RR 6.00 (0.99 to 37.43)	NA
	• Limited to HFS	1 RCT	No	RR 2.19 (1.01 to 4.98)†	NA
	• Age	1 RCT	No	Age did not impact the risk of DVT when comparing LMWH vs. UFH	NA
	• Gender	2 RCTs	No	Gender did not impact risk of DVT when comparing LMWH vs. UFH	NA
	• Ethnicity	1 RCT	No	In white patients, enoxaparin was significantly better at reducing the risk of DVT although this effect was not seen in blacks. Oriental patients and a category called "other" did not have any events therefore the impact could not be evaluated.	NA
	LMWH versus factor Xa inhibitor	5 RCTs	Yes	RR 1.99 (1.57 to 2.51)†	42.5
	• Limited to 2001-present	5 RCTs	Yes	RR 1.99 (1.57 to 2.51)†	42.5
	• Limited to THR	3 RCTs	Yes	OR 1.80 (1.38 to 2.34)†	51.4
	• Limited to TKR	1 RCT	No	RR 2.18 (1.59 to 3.01)†	NA
	• Limited to HFS	1 RCT	No	RR 2.39 (1.75 to 3.28)†	NA
	LMWH versus DTI	1 RCT	No	RR 1.39 (1.15 to 1.68)†	NA
	LMWH versus VKA	5 RCTs	Yes	RR 0.66 (0.55 to 0.79)†	60.9
	• Limited to 2001-present	1 RCT	No	RR 0.57 (0.42 to 0.76)†	NA
	• Limited to THR	3 RCTs	Yes	RR 0.61 (0.44 to 0.84)†	67.6
	• Limited to TKR	3 RCTs	Yes	RR 0.71 (0.57 to 0.87)†	57.2

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Deep vein thrombosis (continued)	LMWH versus mechanical	3 RCTs	Yes	RR 0.90 (0.71 to 1.14)	0
	• Limited to 2001-present	1 RCT	No	RR 0.94 (0.72 to 1.21)	NA
	• Limited to THR	2 RCTs	Yes	RR 0.75 (0.43 to 1.30)	NA
	• Limited to TKR	1 RCT	No	RR 0.94 (0.72 to 1.21)	NA
	UFH versus DTI	2 RCTs	Yes	RR 2.31 (1.34 to 4.00)†	NA
	• Limited to THR	2 RCTs	Yes	RR 2.31 (1.34 to 4.00)†	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	1 RCT	No	RR 2.63 (1.36 to 5.25)†	NA
	VKA versus mechanical	3 RCTs	Yes	RR 1.45 (0.75 to 2.82)	58.5
Asymptomatic DVT	• Limited to THR	3 RCTs	Yes	RR 1.45 (0.75 to 2.82)	58.5
	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	1 RCT	No	OR 1.45 (0.24 to 8.56)	NA
	LMWH versus UFH	2 RCTs	Yes	RR 0.70 (0.43 to 1.16)	NA
	• Limited to THR	2 RCTs	Yes	RR 0.70 (0.43 to 1.16)	NA
	LMWH versus factor Xa inhibitor	0	---	---	---
	LMWH versus DTI	2 RCTs	Yes	RR 0.97 (0.85 to 1.10)	0
	• Limited to 2001-present	2 RCTs	Yes	RR 0.97 (0.85 to 1.10)	0
	• Limited to THR	1 RCT (2 comp)	Yes	RR 1.08 (0.69 to 1.69)	NA
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 0.95 (0.83 to 1.09)	NA
	LMWH versus VKA	1 RCT	No	RR 0.50 (0.28 to 0.88)†	NA
	LMWH versus mechanical	1 RCT	No	OR 1.00 (0.06 to 16.45)	NA
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Symptomatic DVT	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	1 RCT	No	OR 1.91 (0.37 to 9.75)	NA
	LMWH versus UFH	3 RCTs	Yes	OR 0.62 (0.22 to 1.75)	0
		2 RCT	Yes	2 trials evaluated this outcome during the post discharge period and showed OR 1.96 (0.20 to 19.02)	NA
	• Limited to THR	3 RCTs	Yes	OR 0.62 (0.22 to 1.75)	0
	LMWH versus factor Xa inhibitor	6 RCTs	Yes	OR 0.48 (0.21 to 1.12)	0
	• Limited to 2001-present	6 RCTs	Yes	OR 0.48 (0.21 to 1.12)	0
	• Limited to THR	3 RCTs	Yes	OR 0.20 (0.06 to 0.70)†	0
	• Limited to TKR	2 RCTs	Yes	OR 1.01 (0.29 to 3.49)	NA
	• Limited to HFS	1 RCT	No	OR 0.99 (0.06 to 15.83)	NA
	LMWH versus DTI	3 RCTs	Yes	RR 0.98 (0.34 to 2.87)	47.5
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed OR 0.51 (0.14 to 1.91)	NA
	• Limited to 2001-present	3 RCTs	Yes	RR 0.98 (0.34 to 2.87)	47.5
	• Limited to THR	1 RCT (2 comp)	Yes	RR 0.14 (0.02 to 1.03)	NA
	• Limited to TKR	2 RCTs	Yes	RR 1.55 (0.58 to 4.20)	35
	LMWH versus VKA	3 RCTs	Yes	OR 0.87 (0.61 to 1.24)	28.4
	• Limited to 2001-present	1 RCT	No	OR 1.00 (0.06 to 16.09)	NA
	• Limited to THR	2 RCTs	Yes	OR 0.87 (0.60 to 1.24)	52.5
	• Limited to TKR	1 RCT	No	OR 1.00 (0.06 to 16.09)	NA
	LMWH versus mechanical	2 RCTs	No	One trial had no events; the remaining trials showed OR 7.28 (0.14 to 367.07)	NA
	• Limited to THR	2 RCTs	No	One trial had no events; the remaining trials showed OR 7.28 (0.14 to 367.07)	NA
	UFH versus DTI	1 RCT	No	This trial evaluated this outcome during the postdischarge period and showed OR 1.50 (0.26 to 8.74)	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Proximal deep vein thrombosis	Antiplatelet versus VKA	1 RCT	No	RR 0.78 (0.42 to 1.46)	NA
	Antiplatelet versus mechanical	1 RCT	No	OR 0.57 (0.06 to 5.77)	NA
	LMWH versus UFH	9 RCTs	Yes	RR 0.60 (0.38 to 0.93)†	37
	• Limited to THR	6 RCTs	Yes	RR 0.58 (0.39 to 0.86)†	0
	• Limited to TKR	2 RCTs	Yes	RR 0.32 (0.13 to 0.82)†	NA
	• Limited to HFS	1 RCT	No	RR 2.25 (0.95 to 5.61)	NA
	LMWH versus factor Xa inhibitor	5 RCTs	Yes	OR 2.19 (1.52 to 3.16)†	69.9
	• Limited to 2001-present	5 RCTs	Yes	OR 2.19 (1.52 to 3.16)†	69.9
	• Limited to THR	3 RCTs	Yes	OR 1.55 (0.91 to 2.66)	78.2
	• Limited to TKR	1 RCT	No	OR 2.18 (1.04 to 4.57)†	NA
	• Limited to HFS	1 RCT	No	OR 3.80 (1.92 to 7.50)†	NA
	LMWH versus DTI	2 RCTs	Yes	RR 0.91 (0.40 to 2.11)	NA
	• Limited to 2001-present	1 RCT (2 comp)	Yes	RR 0.58 (0.29 to 1.17)	NA
	• Limited to THR	1 RCT	No	OR 1.71 (1.13 to 2.59)†	NA
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 0.58 (0.29 to 1.17)	NA
	LMWH versus VKA	6 RCTs	Yes	RR 0.63 (0.39 to 1.00)	55.3
	• Limited to 2001-present	2 RCTs	Yes	RR 0.43 (0.05 to 4.11)	NA
	• Limited to THR	3 RCTs	Yes	OR 0.67 (0.42 to 1.08)	NA
	• Limited to TKR	4 RCTs	Yes	RR 0.63 (0.30 to 1.34)	68.9
	LMWH versus mechanical	3 RCTs	Yes	RR 0.65 (0.34 to 1.26)	0
	• Limited to 2001-present	1 RCT	No	OR 0.15 (0.02 to 1.05)	NA
	• Limited to THR	2 RCTs	Yes	RR 0.71 (0.36 to 1.40)	NA
	• Limited to TKR	1 RCT	No	OR 0.15 (0.02 to 1.05)	NA
	UFH versus DTI	2 RCTs	Yes	OR 4.74 (2.99 to 7.49)†	NA
	• Limited to THR	2 RCTs	Yes	OR 4.74 (2.99 to 7.49)†	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	3 RCTs	Yes	RR 0.34 (0.16 to 0.73)†	0
	• Limited to THR	3 RCTs	Yes	RR 0.34 (0.16 to 0.73)†	0

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Distal deep vein thrombosis	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	1 RCT	No	RR 1.79 (1.15 to 2.79)†	NA
	LMWH versus UFH	8 RCTs	Yes	RR 0.95 (0.74 to 1.23)	0
	• Limited to THR	5 RCTs	Yes	RR 1.03 (0.58 to 1.83)	0
	• Limited to TKR	2 RCTs	Yes	RR 0.93 (0.69 to 1.24)	NA
	• Limited to HFS	1 RCT	No	OR 1.86 (0.19 to 18.65)	NA
	LMWH versus factor Xa inhibitor	5 RCTs	Yes	RR 2.02 (1.65 to 2.48)†	10
	• Limited to 2001-present	5 RCTs	Yes	RR 2.02 (1.65 to 2.48)†	10
	• Limited to THR	3 RCTs	Yes	OR 1.82 (1.36 to 2.42)†	28.1
	• Limited to TKR	1 RCT	No	RR 2.27 (1.57 to 3.28)†	NA
	• Limited to HFS	1 RCT	No	RR 2.24 (1.59 to 3.17)†	NA
	LMWH versus DTI	1 RCT	No	RR 0.79 (0.67 to 0.93)†	NA
	LMWH versus VKA	2 RCTs	Yes	RR 0.56 (0.43 to 0.73)†	NA
	• Limited to 2001-present	1 RCT	No	RR 0.60 (0.44 to 0.81)†	NA
	• Limited to THR	1 RCT	No	RR 0.48 (0.30 to 0.78)†	NA
	• Limited to TKR	1 RCT	No	RR 0.60 (0.44 to 0.81)†	NA
	LMWH versus mechanical	3 RCTs	Yes	RR 1.00 (0.77 to 1.29)	NA
	• Limited to 2001-present	1 RCT	No	RR 1.01 (0.77 to 1.31)	NA
	• Limited to THR	2 RCTs	No	One trial had no events in the groups compared, the other showed OR 0.84 (0.28 to 2.55)	NA
	• Limited to TKR	1 RCT	No	RR 1.01 (0.77 to 1.31)	NA
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	OR 3.30 (0.91 to 11.91)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Major Bleeding	Antiplatelet versus VKA	1 RCT	No	RR 0.20 (0.03 to 1.23)	NA
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	7 RCTs	Yes	OR 0.57 (0.37 to 0.88)†	37.1
	• Limited to 2001-present	1 RCT	No	OR 7.54 (0.47 to 122.28)	NA
	• Limited to THR	6 RCTs	Yes	OR 0.54 (0.34 to 0.85)†	43.5
	• Limited to TKR	1 RCT	No	OR 0.99 (0.20 to 4.93)	NA
	LMWH versus factor Xa inhibitor	5 RCTs 2 OBS	Yes (RCT)	One trial had no events in the groups compared; the remaining trials showed OR 0.65 (0.48 to 0.89)†; observational data suggested no significant difference	56.6
	• Limited to 2001-present	5 RCTs 1 OBS	Yes (RCT)	One trial had no events in the groups compared; the remaining trials showed OR 0.65 (0.48 to 0.89)†; Observational data suggest no significant difference	56.6
	• Limited to THR	3 RCTs	Yes	One trial had no events in the groups compared; the remaining trials showed OR 0.64 (0.44 to 0.94)†	NA
	• Limited to TKR	1 RCT	No	OR 0.19 (0.06 to 0.58)†	NA
	• Limited to HFS	1 RCT	No	OR 1.04 (0.54 to 2.00)	NA
	LMWH versus DTI	4 RCTs 1 RCT	Yes No	RR 1.12 (0.80 to 1.57) 1 trial evaluated this outcome during the postdischarge period and showed RR 0.51 (0.06 to 4.58)	0 NA
	• Limited to 2001-present	3 RCTs	Yes	RR 1.17 (0.79 to 1.75)	0
	• Limited to THR	2 RCTs	Yes	RR 0.97 (0.64 to 1.48)	0
	• Limited to TKR	2 RCTs	Yes	RR 1.46 (0.82 to 2.59)	0
	LMWH versus VKA	7 RCTs	Yes	OR 1.92 (1.27 to 2.91)†	0
		1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8	NA
	• Limited to 2001-present	2 RCTs	Yes	One trial had no events; the remaining trial showed OR 2.26 (0.75 to 6.83)	NA
	• Limited to THR	3 RCTs	Yes	OR 1.91 (1.11 to 3.29)†	0
		1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8	NA
	• Limited to TKR	4 RCTs	Yes	OR 1.93 (1.01 to 3.67)†	0

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Major Bleeding (continued)	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	1 OBS	No	Observational data suggest major bleeding was significantly increased in patients who received UFH versus injectable or oral factor Xa inhibitor	NA
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Major bleeding leading to reoperation	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	1 RCT	No	No events occurred in the groups compared	NA
	LMWH versus factor Xa inhibitor	4 RCTs	Yes	OR 0.67 (0.28 to 1.61)	0
	• Limited to 2001-present	4 RCTs	Yes	OR 0.67 (0.28 to 1.61)	0
	• Limited to THR	2 RCTs	Yes	OR 0.72 (0.23 to 2.23)	0
	• Limited to TKR	1 RCT	No	OR 0.51 (0.05 to 4.94)	NA
	• Limited to HFS	1 RCT	No	OR 0.66 (0.11 to 3.82)	NA
	LMWH versus DTI	3 RCTs	Yes	RR 1.27 (0.43 to 3.75)	0
	• Limited to 2001-present	3 RCTs	Yes	RR 1.27 (0.43 to 3.75)	0
	• Limited to THR	1 RCT (2 comp)	Yes	RR 1.21 (0.29 to 5.08)	NA
	• Limited to TKR	2 RCTs	Yes	RR 1.36 (0.27 to 7.03)	0
	LMWH versus VKA	2 RCTs	No	One trial had no events; the remaining trial showed OR 7.61 (0.15 to 383.70)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	1 RCT	No	OR 7.61 (0.15 to 383.70)	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.51 (0.10 to 2.55)	NA
	• Limited to THR	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.51 (0.10 to 2.55)	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Minor Bleeding	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	5 RCTs	Yes	RR 0.90 (0.63 to 1.28)	9.9
	• Limited to 2001-present	1 RCT	No	RR 0.25 (0.03 to 2.16)	NA
	• Limited to THR	4 RCTs	Yes	OR 0.92 (0.57 to 1.51)	31.4
	• Limited to TKR	1 RCT	No	RR 0.87 (0.60 to 1.25)	NA
	LMWH versus factor Xa inhibitor	2 RCTs	Yes	OR 0.57 (0.35 to 0.94)†	NA
	• Limited to 2001-present	2 RCTs	Yes	OR 0.57 (0.35 to 0.94)†	NA
	• Limited to THR	1 RCT	No	OR 0.85 (0.27 to 2.62)	NA
	• Limited to HFS	1 RCT	No	OR 0.52 (0.30 to 0.91)†	NA
	LMWH versus DTI	3 RCTs	Yes	RR: 1.07 (0.89 to 1.29)	0
		1 RCT	No	1 trial evaluated this outcome during the postdischarge period and showed a RR 0.54 (0.15 to 1.94)	NA
	• Limited to 2001-present	3 RCTs	Yes	RR 1.07 (0.89 to 1.29)	0
	• Limited to THR	1 RCT (2 comp)	Yes	RR 1.04 (0.79 to 1.37)	NA
	• Limited to TKR	2 RCTs	Yes	RR 1.10 (0.86 to 1.40)	0
	LMWH versus VKA	7 RCTs	Yes	RR 1.23 (1.06 to 1.43)†	0
		1 RCT (2 comp)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8	NA
	• Limited to 2001-present	2 RCTs	Yes	RR 1.25 (0.85 to 1.83)	NA
	• Limited to THR	3 RCTs	Yes	RR 1.26 (0.85 to 1.86)	27.8
		1 RCT (2 comp)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8	NA
	• Limited to TKR	4 RCTs	Yes	RR 1.17 (0.95 to 1.43)	0
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	2 RCTs	Yes	OR 0.80 (0.26 to 2.41)	NA
	• Limited to THR	2 RCTs	Yes	OR 0.80 (0.26 to 2.41)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Surgical site bleeding	Antiplatelet versus VKA	1 OBS	No	Observational data suggest no significant difference	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	3 RCTs	Yes	OR 0.92 (0.46 to 1.82)	41.1
	• Limited to 2001-present	1 RCT	No	RR 0.75 (0.20 to 2.86)	NA
	• Limited to THR	2 RCTs	Yes	RR 0.63 (0.26 to 1.55)	3.1
	• Limited to TKR	1 RCT	No	OR 1.78 (0.61 to 5.14)	NA
	LMWH versus factor Xa inhibitor	1 RCT	No	OR 0.72 (0.45 to 1.17)	NA
	LMWH versus DTI	1 RCT	No	RR 4.35 (1.51 to 12.54)†	NA
	LMWH versus VKA	2 RCT	Yes	OR 2.63 (1.31 to 5.28)†	NA
	• Limited to 2001-present	1 RCT	No	OR 2.05 (0.80 to 5.29)	NA
	• Limited to THR	1 RCT	No	OR 3.35 (1.27 to 9.84)†	NA
	• Limited to TKR	1 RCT	No	OR 2.05 (0.80 to 5.29)	NA
	• Major surgical site bleeding	2 RCTs	Yes	OR 2.51 (1.38 to 4.54)†	NA
		1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed a RR 1.72 (1.02 to 2.92)† on days 0-1 and a RR 2.72 (0.59 to 12.44) on days 2-8	NA
	• Minor surgical site bleeding	2 RCTs	Yes	OR 1.34 (0.91 to 1.97)	NA
		1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed an OR 7.42 (0.15 to 373.92) on days 0-1 and an OR 7.43 (0.46 to 119.03) on days 2-8	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	1 RCT	No	OR 0.87 (0.31 to 2.43)	NA
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---
Bleeding leading to infection		0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Bleeding leading to transfusion	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	0	---	---	---
	LMWH versus factor Xa inhibitor	0	---	---	---
	LMWH versus DTI	2 RCTs	Yes	RR 1.00 (0.59 to 1.69)	0
	• Limited to 2001-present	2 RCTs	Yes	RR 1.00 (0.59 to 1.69)	0
	• Limited to THR	1 RCT (2 comp)	Yes	RR 1.19 (0.46 to 3.10)	NA
	• Limited to TKR	1 RCT (2 comp)	Yes	RR 0.71 (0.26 to 1.98)	NA
	LMWH versus VKA	1 RCT	No	OR 1.71 (0.42 to 6.90)	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Heparin induced thrombocytopenia	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	3 RCTs	Yes	OR 0.13 (0.03 to 0.43)†	0
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	3 RCTs	Yes	OR 0.13 (0.03 to 0.43)†	0
	LMWH versus factor Xa inhibitor	0	---	---	---
	LMWH versus DTI	0	---	---	---
	LMWH versus VKA	1 RCT	No	No events occurred in the groups compared	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Discomfort	Antiplatelet versus VKA	0	---	---	--
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	0	---	---	--
	LMWH versus factor Xa inhibitor	0	---	---	--
	LMWH versus DTI	0	---	---	--
	LMWH versus VKA	0	---	---	--
	LMWH versus mechanical	1 RCT	No	RR 0.49 (0.29 to 0.82)†	NA
	UFH versus DTI	0	---	---	--
	UFH versus factor Xa inhibitor	0	---	---	--
	UFH versus mechanical	0	---	---	--
	VKA versus mechanical	0	---	---	--
Readmission	Antiplatelet versus VKA	0	---	---	--
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	2 RCT	Yes	RR 0.82 (0.20 to 3.38)	14.2
	• Limited to 2001-present	1 RCT	No	OR 7.54 (0.47 to 122.23)	NA
	• Limited to THR	2 RCT	Yes	RR 0.82 (0.20 to 3.38)	14.2
	LMWH versus factor Xa inhibitor	0	---	---	---
	LMWH versus DTI	0	---	---	---
	LMWH versus VKA	0	---	---	---
	LMWH versus mechanical	2 RCT	Yes	OR 0.83 (0.22 to 3.11)	NA
	• Limited to 2001-present	1 RCT	No	OR 0.78 (0.17 to 3.50)	NA
	• Limited to THR	1 RCT	No	OR 0.78 (0.17 to 3.50)	NA
	• Limited to TKR	1 RCT	No	OR 1.03 (0.06 to 16.52)	NA
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	1 RCT	No	OR 0.15 (0.003 to 7.58)	NA

Table 12. Summary of results for Key Question 5: what is the comparative efficacy and safety between classes of pharmacologic and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I ² (%)
Reoperation	Antiplatelet versus VKA	0	---	---	---
	Antiplatelet versus mechanical	0	---	---	---
	LMWH versus UFH	0	---	---	---
	LMWH versus factor Xa inhibitor	1 RCT	No	RR 0.25 (0.04 to 1.63)	NA
	LMWH versus DTI	0	---	---	---
	LMWH versus VKA	2 RCT	No	One trial had no events in the groups compared, the remaining trial showed RR 0.85 (0.59 to 1.22)	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	1 RCT	No	RR 0.85 (0.59 to 1.22)	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
	LMWH versus mechanical	0	---	---	---
	UFH versus DTI	0	---	---	---
	UFH versus factor Xa inhibitor	0	---	---	---
	UFH versus mechanical	0	---	---	---
	VKA versus mechanical	0	---	---	---

comp = comparison(s); DTI = direct thrombin inhibitor; HFS = hip fracture surgery; LMWH = low molecular weight heparin; NA = Not Applicable; OBS = observational; OR = Peto's Odds Ratio; RCT = Randomized Controlled Trial; RR = Relative Risk; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKA = vitamin K antagonist

*All base case analyses are represented in the table without a bullet, bulleted analyses are subgroup analyses. When only 1 trial or study was available subgroup analyses were not run. Subgroup analyses with no available data are not represented in this table.

†Statistically significant.

--- No data.

Key Question 6

In patients undergoing major orthopedic surgery (total hip and knee replacement, hip fracture surgery), what is the comparative efficacy of individual agents within classes (injectable low molecular weight heparin or mechanical) on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Points

- The literature base for intraclass comparisons of therapy is not as extensive as the interclass comparisons in Key Question 5 and therefore for most outcomes was insufficient to determine comparative efficacy and safety.
- Venous thromboembolism (symptomatic, major), postthrombotic syndrome, health related quality of life, major bleeding leading to reoperation, bleeding leading to infection, bleeding leading to transfusion, discomfort, reoperation, or readmission outcomes could not be evaluated due to lack of trials or studies evaluating these endpoints.
- For pulmonary embolism, the single trial comparing low molecular weight heparins and two of the three trials comparing mechanical prophylaxis had no events in either group. In the one trial with events, no significant differences were found between the Venaflow and Kendall devices, although the confidence intervals were very large.
- For fatal pulmonary embolism, one of two trials comparing low molecular weight heparins and all three trials comparing mechanical prophylaxis had no events in either group. In the one trial with events, no significant differences were found between enoxaparin and tinzaparin although the confidence intervals were very large.
 - One observational trial comparing mechanical prophylactic devices also did not have any fatal pulmonary embolism events.
- For nonfatal pulmonary embolism, one of two trials comparing low molecular weight heparins and two of three trials comparing mechanical prophylaxis had no events in either group. In the one low molecular weight heparin trial with events, no significant differences were found between enoxaparin and tinzaparin although the confidence intervals were very large. In the one mechanical prophylaxis trial, no significant differences were found between the Venaflow and Kendall devices, although the confidence intervals were very large.
 - One observational study comparing the ActiveCare system versus the Flowtron pump mechanical devices found no significant differences between groups in the occurrence of nonfatal pulmonary embolism. Very low rates occurred in both groups (0 percent versus 0.7 percent, $p=0.459$).

- One trial found no difference in mortality between enoxaparin and tinzaparin while another trial found no difference between the Venaflow and Kendall devices. The confidence intervals for these evaluations were very large.
 - No events occurred in an observational study comparing mechanical prophylaxis devices.
- For mortality due to bleeding, one trial comparing low molecular weight heparins and one trial and one observational study evaluated the impact of mechanical prophylaxis strategies. No events occurred in either group in these evaluations.
- More data are available regarding the comparison of drugs within a class on the occurrence of deep venous thrombosis, proximal deep venous thrombosis, and distal deep venous thrombosis.
 - No difference in the occurrence of deep venous thrombosis occurred in the pooled analysis comparing enoxaparin versus either tinzaparin or dalteparin.
 - The Venaflow pneumatic compression device significantly reduced the occurrence of deep venous thrombosis versus the Kendall pneumatic compression device in the only trial.
 - The same results were found when trials were limited to the years 2001-present and to total knee replacement surgery.
 - Intermittent compression stockings significantly reduce the occurrence of deep venous thrombosis versus graduated compression stockings in the only trial.
 - The same results were found when trials were limited to the years 2001-present and to total hip replacement and total knee replacement surgery.
 - In the only observational study, two intermittent compression devices were compared (ActiveCare system versus Flowtron excel pump) and found to have a similar occurrence of deep venous thrombosis.
- For asymptomatic deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and dalteparin but no trials or observational studies compared mechanical devices.
- For symptomatic deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and tinzaparin but neither of the two trials comparing mechanical devices had events in either group.
- For proximal deep venous thrombosis, two trials compared low molecular weight heparins and found no significant difference between enoxaparin and either dalteparin or tinzaparin. In one trial comparing two different intermittent compression devices (Venaflow versus Kendall), no significant difference in the occurrence of proximal deep venous thrombosis occurred. Neither of the two trials comparing intermittent compressions stockings versus graduated compression stocking found a significant difference in the occurrence of proximal deep venous thrombosis.
- For distal deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and tinzaparin. In one trial, the occurrence of distal deep venous thrombosis was significantly lower with the Venaflow intermittent compression device than with the Kendall intermittent compression device. In a trial, the occurrence of distal deep venous thrombosis was lower with intermittent compression stockings versus graduated compression stockings. Both of the mechanical intervention trials were conducted from 2001-present and included patients with total hip and total knee replacement surgery.

- For major bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. No trials or studies evaluated the impact of mechanical interventions on this endpoint.
- For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. No trials or studies evaluated mechanical interventions on this endpoint.
- For surgical site bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. No trials or studies evaluated the impact of mechanical interventions on this endpoint.
- For heparin induced thrombocytopenia, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. No trials or studies evaluated mechanical interventions on this endpoint.

Detailed Analysis

Study Design and Characteristics

Five randomized controlled trials (N=1,285) and one controlled observational study (N=1,577) evaluated the comparative efficacy within the classes of injectable low molecular weight heparin agents and mechanical devices.^{27,108,110,113,141,149} All five trials were published as full text manuscripts. Two trials compared injectable low molecular weight heparin agents (N=631),^{27,108} two trials compared mechanical prophylaxes (N=523)^{110,141} and one trial compared mechanical prophylaxes with all patients receiving enoxaparin prophylaxis also (N=131).¹¹³ The observational study compared mechanical prophylaxes (N=1,577).¹⁴⁹ Two trials enrolled patients who had total hip replacement surgery (N= 599),^{27,112} one trial enrolled patients who had total knee replacement surgery (N= 423),¹¹⁰ one trial enrolled patients who had hip fracture surgery (N=132),¹⁰⁸ and one trial enrolled patients who had either total hip replacement or total knee replacement surgery (N=131).¹¹³ The observational study also enrolled patients who had total hip replacement or total knee replacement surgery (N=1,577).¹⁴⁹ The earliest study was published in 1998¹⁴¹ and the most recent study was published in 2009.¹⁴⁹ The duration of followup ranged from postoperative period to 180 days. Four trials received funding from the industry,^{27,110,113,141} one trial received funding from government and foundation¹⁰⁸ and the observational study was unfunded.¹⁴⁹

The mean age of enrolled patients ranged from 63.0 years to 77 years. Females represented between 55.24 and 78.79 percent of the enrolled populations. The mean weight ranged from 71.0 to 87.7 kilograms. Few patients enrolled had a history of venous thromboembolism ranging from 3.1 to 9.0 percent. One study reported presence of varicosity ranging from 61.9 to 66.18 percent. The percent of patients with a history of malignancy ranged from 3.1 to 6.1 percent.

Seventy-seven to 100 percent of patients underwent primary surgery and one trial reported the percent of patients who had cemented fixation during surgery ranging from 42.65 to 46.03 percent. Mean duration of surgery ranged from 69.0 to 93.0 minutes and the mean duration of anesthesia ranged from 133 to 161 minutes. Use of general anesthesia ranged from 11.98 to 27.94 percent and use of regional anesthesia ranged from 72.0 to 100.0 percent of patients. The mean length of hospital stay was reported by the observational study ranging from 4.2 to 5 days.

Outcome Evaluations

A summary of the results is presented in Table 13.

Symptomatic Objectively Confirmed Venous Thromboembolism

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Major Venous Thromboembolism

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Pulmonary Embolism

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between enoxaparin and dalteparin on pulmonary embolism in patients who had hip fracture surgery although no events occurred therefore the risk of pulmonary embolism could not be calculated.¹⁰⁸

Mechanical Prophylaxis

Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on pulmonary embolism in patients who had major orthopedic surgery.^{110,113,141} Two trials that evaluated intermittent pneumatic compression versus graduated compression stockings did not have events occur in the groups compared therefore the risk of pulmonary embolism could not be evaluated.^{113,141} One trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery.¹¹⁰ In this trial, the odds of pulmonary embolism were not significantly different [OR 0.14 (0.003 to 7.18)] in patients who received the Venaflow device versus the Kendall device.

Fatal Pulmonary Embolism

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on fatal pulmonary embolism in patients who had major orthopedic surgery.^{27,108} One trial was excluded from the analysis because no events occurred.¹⁰⁸ The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip replacement surgery.²⁷ In this trial, the odds of fatal pulmonary embolism were not significantly different [OR 7.48 (0.15 to 376.94)] in patients who received enoxaparin versus tinzaparin.

Mechanical Prophylaxis

Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on pulmonary embolism in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.^{110,113,141}

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on fatal pulmonary embolism in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.¹⁴⁹

Nonfatal Pulmonary Embolism

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{27,108} One trial was excluded from the analysis because no events occurred.¹⁰⁸ The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip replacement surgery.²⁷ In this trial, the odds of nonfatal pulmonary embolism were not significantly different [OR 1.01 (0.06 to 16.23)] in patients who received enoxaparin versus tinzaparin.

Mechanical Prophylaxis

Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{110,113,141} Two trials that evaluated intermittent pneumatic compression versus graduated compression stockings did not have events occur in the groups compared therefore the risk of pulmonary embolism could not be evaluated.^{113,141} One trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery.¹¹⁰ In this trial, in patients who received the Venaflow device versus the Kendall device, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 7.18)].

One controlled observational study evaluated comparative efficacy between individual mechanical prophylaxis devices on nonfatal pulmonary embolism in patients who had major orthopedic surgery.¹⁴⁹ Two intermittent pneumatic compression devices were compared in patients who had either total hip or knee replacement surgery; ActiveCare continuous enhanced

circulatory system versus Flowtron excel pump. Patients also received enoxaparin (30mg twice daily for knee and 40mg daily for hip surgery) starting 12-24 hours postoperatively at the discretion of the clinical team however the percent of patients that did receive enoxaparin in each group was not reported. There was no significant difference in the percent of patients that developed a nonfatal pulmonary embolism in the ActiveCare group versus the Flowtron group (0 percent versus 0.7 percent, $p=0.459$).

Postthrombotic Syndrome

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Mortality

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on mortality in patients who had major orthopedic surgery.²⁷ This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of mortality were not significantly different [OR 7.48 (0.15 to 376.94)].

Mechanical Prophylaxis

One randomized controlled trial evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.¹¹⁰ This trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery. In patients who received the Venaflow device versus the Kendall device, the odds of mortality were not significantly different [OR 0.14 (0.003 to 7.18)].

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on mortality in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality could not be calculated.¹⁴⁹

Mortality Due to Bleeding

Low Molecular Weight Heparin Agents

One randomized controlled evaluated the comparative efficacy between individual low molecular weight heparin agents on mortality due to bleeding in patients who had major

orthopedic surgery although no events occurred therefore the risk of mortality due to bleeding could not be calculated.²⁷

Mechanical Prophylaxis

One randomized controlled trial evaluated the comparative efficacy between individual mechanical prophylaxis devices on mortality due to bleeding in patients who had major orthopedic surgery although no events occurred therefore the risk of mortality due to bleeding could not be calculated.¹¹⁰

One controlled observational study evaluated comparative efficacy between individual mechanical prophylaxis devices on mortality due to bleeding in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality due to bleeding could not be calculated.¹⁴⁹

Health-Related Quality of Life

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Deep Vein Thrombosis

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on deep vein thrombosis in patients who had major orthopedic surgery.^{27,108} The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the risk of deep vein thrombosis was not significantly different [RR 0.93 (0.64 to 1.33)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the risk of deep vein thrombosis was not significantly different [RR 1.75 (0.64 to 4.84)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the risk of deep vein thrombosis was not significantly different [RR 1.05 (0.64 to 1.71)] (Appendix G Figure 204). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

Mechanical Prophylaxis

Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on deep vein thrombosis in patients who had major orthopedic surgery.^{110,113} The first trial by Lachiewicz and colleagues in 2004 compared two intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on in which patients received the Venaflow device versus the Kendall device for prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.46 (0.26 to 0.79), NNT 13].

The second trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.¹¹³ In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of deep vein thrombosis was significantly decreased [RR 0.09 (0.01 to 0.92), NNT 7]. In the patients who had total knee replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of deep vein thrombosis was significantly decreased [RR 0.03 (0.004 to 0.31), NNT 3]. When pooling these two surgical populations to compare intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, in patients who had major orthopedic surgery, the risk of deep vein thrombosis was significantly decreased [RR 0.06 (0.01 to 0.42), NNT 3 to 7] (Appendix G Figure 205). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on deep vein thrombosis in patients who had major orthopedic surgery.¹⁴⁹ Two intermittent pneumatic compression devices were compared in patients who had either total hip or knee replacement surgery; ActiveCare continuous enhanced circulatory system versus Flowtron excel pump. Patients also received enoxaparin (30mg twice daily for knee and 40mg daily for hip surgery) starting 12-24 hours postoperatively at the discretion of the clinical team however the percent of patients that did receive enoxaparin in each group was not reported. In patients who received the ActiveCare device versus the Flowtron device, there was no significant difference in the risk of deep vein thrombosis (1.35 percent versus 3.62 percent, $p=0.119$).

Asymptomatic Deep Vein Thrombosis

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.¹⁰⁸ This trial by the TIFDED study group in 1999 compared enoxaparin to dalteparin in patients who had hip fracture surgery. In this trial, the risk of asymptomatic deep vein thrombosis was not significantly different [RR 1.75 (0.64 to 4.84)] in patients who received enoxaparin versus dalteparin.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Symptomatic Deep Vein Thrombosis

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{27,108} One trial was excluded from the analysis because no events occurred.¹⁰⁸ The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip replacement surgery.²⁷ In this trial, the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.51 (0.26 to 8.79)] in patients who received enoxaparin versus tinzaparin.

Mechanical Prophylaxis

Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{110,141} One trial evaluated this outcome during the post discharge period.¹¹⁰ However, in both trials, no events occurred in the groups compared therefore the risk of symptomatic deep vein thrombosis could not be calculated.^{110,141}

Proximal Deep Vein Thrombosis

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{27,108} The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, the odds of proximal deep vein thrombosis were not significantly different [OR 1.12 (0.60 to 2.08)] in patients who received enoxaparin versus dalteparin. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, the odds of proximal deep vein thrombosis were not significantly different [OR 0.73 (0.12 to 4.34)] in patients who received enoxaparin versus tinzaparin. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the risk of proximal deep vein thrombosis was not significantly different [RR 1.06 (0.62 to 1.81)] (Appendix G Figure 206). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

Mechanical Prophylaxis

Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{110,113,141} The first trial by Lachiewicz and colleagues in 2004 compared two

intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on, in which patients received the Venaflow device versus the Kendall device for prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.24 (0.05 to 1.08)].

The second trial by Ryan and colleagues in 1998 compared intermittent pneumatic compression versus graduated compression stockings in patients who had total hip replacement surgery.¹⁴¹ In this trial, in patients who received intermittent pneumatic compression versus graduated compression stockings the risk of proximal deep vein thrombosis was not significantly different [RR 0.36 (0.13 to 1.00)].

The third trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.¹¹³ In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the odds of proximal deep vein thrombosis were not significantly different [OR 0.11 (0.002 to 5.78)]. In the patients who had total knee replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the odds of proximal deep vein thrombosis were not significantly different [OR 0.14 (0.003 to 6.82)]. When pooling these two surgical populations to evaluate the comparison of intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, in patients who had major orthopedic surgery, the odds of proximal deep vein thrombosis were not significantly different [OR 0.12 (0.01 to 1.99)] (Appendix G Figure 207). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

Distal Deep Vein Thrombosis

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on distal deep vein thrombosis in patients who had major orthopedic surgery.²⁷ This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the risk of distal deep vein thrombosis was not significantly different [RR 0.78 (0.46 to 1.34)].

Mechanical Prophylaxis

Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on distal deep vein thrombosis in patients who had major orthopedic surgery.^{110,113} The first trial by Lachiewicz and colleagues in 2004 compared two intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on

in which patients received the Venaflow device versus the Kendall device for prophylaxis, the risk of distal deep vein thrombosis was significantly decreased [RR 0.52 (0.29 to 0.93), NNT 35].

The second trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.¹¹³ In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of distal deep vein thrombosis was not significantly different [RR 0.15 (0.01 to 1.53)]. In the patients who had total knee replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of distal deep vein thrombosis was significantly decreased [RR 0.04 (0.004 to 0.33), NNT 3]. When pooling these two surgical populations to compare intermittent pneumatic compression versus graduated compression stockings, both in combination with enoxaparin in patients who had major orthopedic surgery, the risk of distal deep vein thrombosis was significantly decreased [RR 0.07 (0.01 to 0.54), NNT 3 to 11] (Appendix G Figure 208). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

Major Bleeding

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on major bleeding in patients who had major orthopedic surgery.^{27,108} The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the odds of major bleeding were not significantly different [OR 1.98 (0.40 to 9.91)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of major bleeding were not significantly different [OR 1.97 (0.20 to 19.25)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the odds of major bleeding were not significantly different [RR 1.98 (0.53 to 7.37)] (Appendix G Figure 210). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trials were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Major Bleeding Leading to Reoperation

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Minor Bleeding

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on minor bleeding in patients who had major orthopedic surgery.²⁷ This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of minor bleeding were not significantly different [OR 1.67 (0.84 to 3.36)].

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Surgical Site Bleeding

Low Molecular Weight Heparin Agents

Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on surgical site bleeding in patients who had major orthopedic surgery.^{27,108} The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the odds of surgical site bleeding were not significantly different [OR 1.98 (0.40 to 9.91)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of surgical site bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the odds of surgical site bleeding were not significantly different [RR 1.35 (0.30 to 5.97)] (Appendix G Figure 211). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Infection

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Transfusion

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Heparin-Induced Thrombocytopenia

Low Molecular Weight Heparin Agents

One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on heparin induced thrombocytopenia in patients who had major orthopedic surgery.²⁷ This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of heparin induced thrombocytopenia were not significantly different [OR 7.48 (0.15 to 376.94)].

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Discomfort

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Readmission

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Reoperation

Low Molecular Weight Heparin Agents

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.

Strength of Evidence and Applicability of the Body of Evidence

Key Question 6 compared agents within the low molecular weight heparin class as well as within mechanical devices. Overall there were very few comparative studies and those evaluated had very low event rates. Therefore the majority of outcomes were rated with insufficient strength of evidence. There was insufficient evidence for all outcomes when comparing specific mechanical devices, as although two studies compared specific mechanical devices, they each compared different devices. When compared with graduated compression devices, intermittent pneumatic compression devices decreased the risk of overall and distal deep vein thrombosis, while there was no difference in the risk of proximal deep vein thrombosis, each with a low strength of evidence. When comparing enoxaparin to other low molecular weight heparins (dalteparin or tinzaparin), there was no difference in the risk of overall or proximal deep vein

thrombosis, or in the odds of surgical site bleeding, all with low strength of evidence. When comparing enoxaparin to other low molecular weight heparins (dalteparin or tinzaparin), there was moderate strength of evidence that there was no difference in the risk of major bleeding, while all other outcomes were rated insufficient.

Overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data. The specificity of the comparisons within the given studies applicability was rated low for the great majority of outcomes and comparisons. Data were often highly applicable to a specific device comparison within one or two of the major orthopedic surgeries. Hip fracture surgery was generally not evaluated. In comparison of low molecular weight heparins, the majority of trials were conducted outside of the United States and for a given outcome, usually either tinzaparin or dalteparin were compared with enoxaparin (not both) in one major orthopedic surgery.

Table 13. Summary of results of Key Question 6: what is the comparative efficacy and safety within class of low-molecular weight heparin agents and mechanical prophylaxis methods in major orthopedic surgery?*

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Symptomatic objectively confirmed VTE	Enoxaparin versus LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Major VTE	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
PE	Enoxaparin versus other LMWH	1 RCT	No	No events occurred in the groups compared	NA
	IPC versus IPC	1 RCT	No	OR 0.14 (0.003 to 7.18)	NA
	IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
Fatal PE	Enoxaparin versus other LMWH	2 RCTs	No	One trial had no events; remaining one trial showed OR 7.48 (0.15 to 376.94)	NA
	• Limited to THR	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
	• Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
	IPC versus IPC	1 RCT, 1 OBS	No	No events occurred in the groups compared	NA
	IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
Nonfatal PE	Enoxaparin versus other LMWH	2 RCTs	No	One trial had no events; remaining one trial showed OR 1.01 (0.06 to 16.23)	NA
	• Limited to THR	1 RCT	No	OR 1.01 (0.06 to 16.23)	NA
	• Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
	IPC versus IPC	1 RCT, 1 OBS	No	OR 0.14 (0.003 to 7.18); observational data suggest no significant difference in the percent of patients that developed a nonfatal PE in the ActiveCare group versus the Flowtron group	NA
	IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
	• Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
	• Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA

Table 13. Summary of results of Key Question 6: what is the comparative efficacy and safety within class of low-molecular weight heparin agents and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
PTS	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Mortality	Enoxaparin versus other LMWH	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
	IPC versus IPC	1 RCT, 1 OBS	No	OR 0.14 (0.003 to 7.18); In the observational study, no events occurred in the groups compared	NA
	IPC versus GCS	0	---	---	---
Mortality due to bleeding	Enoxaparin versus other LMWH	1 RCT	No	No events occurred in the groups compared	NA
	IPC versus IPC	1 RCT, 1 OBS	No	No events occurred in the groups compared	NA
	IPC versus GCS	0	---	---	---
HRQOL	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
DVT	Enoxaparin versus other LMWH	2 RCTs	Yes	RR 1.05 (0.64 to 1.71)	NA
	• Limited to THR	1 RCT	No	RR 1.75 (0.64 to 4.84)	NA
	• Limited to HFS	1 RCT	No	RR 0.93 (0.64 to 1.33)	NA
	IPC versus IPC	1 RCT, 1 OBS	No	1 trial evaluated this outcome in total knees operated and showed RR 0.46 (0.26 to 0.79); observational data suggest no significant difference in the risk of DVT in patients who received ActiveCare device versus Flowtron	NA
	IPC versus GCS	1 RCT (2 comp)	Yes	RR 0.06 (0.01 to 0.42)	NA
	• Limited to 2001-present	1 RCT (2 comp)	Yes	RR 0.06 (0.01 to 0.42)	NA
	• Limited to THR	1 RCT (1 comp)	No	RR 0.09 (0.01 to 0.92)	NA
	• Limited to TKR	1 RCT (1 comp)	No	RR 0.03 (0.004 to 0.31)	NA
	• Limited to HFS	0	---	---	---
Asymptomatic DVT	Enoxaparin versus other LMWH	1 RCT	No	RR 1.75 (0.64 to 4.84)	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---

Table 13. Summary of results of Key Question 6: what is the comparative efficacy and safety within class of low-molecular weight heparin agents and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Symptomatic DVT	Enoxaparin versus other LMWH	2 RCTs	No	1 trial had no events; remaining trial showed OR 1.51 (0.26 to 8.79)	NA
	• Limited to THR	1 RCT	No	OR 1.51 (0.26 to 8.79)	NA
	• Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	1 RCT	No	No events occurred in the groups compared	NA
Proximal DVT	Enoxaparin versus other LMWH	2 RCTs	Yes	RR 1.06 (0.62 to 1.81)	NA
	• Limited to THR	1 RCT	No	OR 0.73 (0.12 to 4.34)	NA
	• Limited to HFS	1 RCT	No	OR 1.12 (0.60 to 2.08)	NA
	IPC versus IPC	1 RCT	No	1 trial evaluated this outcome in total knees operated and showed OR 0.24 (0.05 to 1.08)	NA
	IPC versus GCS	2 RCTs	No	1 trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.12 (0.01 to 1.99)	
	• Limited to 2001-present	1 RCT (2 comp)	Yes	OR 0.12 (0.01 to 1.99)	NA
	• Limited to THR	2 RCTs	No	1 trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.11 (0.002 to 5.78)	NA
	• Limited to TKR	1 RCT	No	OR 0.14 (0.003 to 6.82)	NA
Distal DVT	Enoxaparin versus other LMWH	1 RCT	No	RR 0.78 (0.46 to 1.34)	NA
	IPC versus IPC	1 RCT	No	1 trial evaluated this outcome in total knees operated and showed RR 0.52 (0.29 to 0.93)	NA
	IPC versus GCS	1 RCT (2 comp)	Yes	RR 0.07 (0.01 to 0.54)	NA
	• Limited to 2001-present	1 RCT (2 comp)	Yes	RR 0.07 (0.01 to 0.54)	NA
	• Limited to THR	1 RCT (1 comp)	No	RR 0.15 (0.01 to 1.53)	NA
	• Limited to TKR	1 RCT (1 comp)	No	RR 0.04 (0.004 to 0.33)	NA

Table 13. Summary of results of Key Question 6: what is the comparative efficacy and safety within class of low-molecular weight heparin agents and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Major bleeding	Enoxaparin versus other LMWH	2 RCT	Yes	RR 1.98 (0.53 to 7.37)	NA
	• Limited to THR	1 RCT	No	OR 1.97 (0.20 to 19.25)	NA
	• Limited to HFS	1 RCT	No	OR 1.98 (0.40 to 9.91)	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Major bleeding leading to reoperation	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Minor bleeding	Enoxaparin versus other LMWH	1 RCT	No	OR 1.67 (0.84 to 3.36)	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Surgical site bleeding	Enoxaparin versus other LMWH	2 RCT	Yes	RR 1.35 (0.30 to 5.97)	NA
	• Limited to THR	1 RCT	No	OR 0.14 (0.003 to 6.82)	NA
	• Limited to HFS	1 RCT	No	OR 1.98 (0.40 to 9.91)	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Bleeding leading to infection	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Bleeding leading to transfusion	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
HIT	Enoxaparin versus other LMWH	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Discomfort	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---

Table 13. Summary of results of Key Question 6: what is the comparative efficacy and safety within class of low-molecular weight heparin agents and mechanical prophylaxis methods in major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Readmission	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---
Reoperation	Enoxaparin versus other LMWH	0	---	---	---
	IPC versus IPC	0	---	---	---
	IPC versus GCS	0	---	---	---

comp = comparison(s); DVT = deep vein thrombosis; GCS = graduated compression stockings; HIT = heparin induced thrombocytopenia; HFS = hip fracture surgery; HRQOL = health related quality of life; IPC = intermittent pneumatic compression; LMWH = low molecular weight heparin; NA = Not Applicable; OBS = observational; OR = Peto's Odds Ratio; PE = pulmonary embolism; PTS = post thrombotic syndrome; RCT = Randomized Controlled Trial; RR = Relative Risk; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

*All base case analyses are represented in this table. If only 1 trial was available subgroup analyses were not run. Only subgroup analyses with available data are represented in this table.

--- No data.

Key Question 7

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities vs. single modality on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Points

- There was insufficient evidence for all outcomes when comparing two prophylactic strategies (pharmacologic plus mechanical) mechanical prophylaxis with the exception of proximal deep vein thrombosis. There was low strength of evidence that the combination has no significant impact on proximal deep vein thrombosis compared to mechanical prophylaxis alone [RR0.78 (0.35 to 1.74)].
- There is moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of deep venous thrombosis versus pharmacologic prophylaxis alone in patients with major orthopedic surgery [RR 0.48 (0.32 to 0.72)].
 - The impact of pharmacological plus mechanical prophylaxis versus mechanical prophylaxis cannot be discerned due to a lack of events in experimental groups.
- The use of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical does not significantly impact subclasses of deep venous thromboses (asymptomatic, proximal, or distal deep) in patients with major orthopedic surgery
- The use of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical does not significantly impact nonfatal pulmonary embolism, mortality, asymptomatic deep venous thrombosis, symptomatic deep venous thrombosis, proximal deep venous thrombosis, or distal deep venous thrombosis in patients with major orthopedic surgery
- The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis on major bleeding or minor bleeding could not be determined since no events occurred in the two comparative groups in the available trials.
 - No data are available to evaluate the comparative impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis on major bleeding or minor bleeding.
- No data are available to evaluate the comparative impact of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical on symptomatically confirmed or major venous thromboembolism, postthrombotic syndrome, health related quality of life, major bleeding leading to reoperation, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin

induced thrombocytopenia, discomfort, reoperation, or readmission in patients with major orthopedic surgery.

- The comparative impact of dual prophylactic modalities versus a single modality on fatal pulmonary embolism, or mortality due to bleeding could not be determined since no events occurred in the two comparative groups in the available trials.

Detailed Analysis

Study Design and Characteristics

Six randomized controlled trials (N=995) and no controlled observation studies evaluated the impact of combined pharmacologic and mechanical modalities versus single modality on final health, intermediate and adverse outcomes.^{114-117,133,134} All six trials were published as full text manuscripts. Four of the randomized controlled trials (N=708) compared pharmacologic prophylaxis in combination with a mechanical prophylaxis versus pharmacologic prophylaxis alone,^{114-116,133} one of the randomized controlled trials (N=212) compared pharmacologic prophylaxis in combination with a mechanical prophylaxis versus mechanical prophylaxis alone,¹¹⁷ and one randomized controlled trial (N=75) included both comparisons.¹³⁴ Four trials enrolled exclusively patients who had total hip replacement surgery (N= 596),^{115,117,133,134} one trial enrolled exclusively patients who had total knee replacement surgery (N=122),¹¹⁶ and one trial enrolled both patient populations although reported results separately (N=277).¹¹⁴ No trials enrolled patients who had hip fracture surgery. The earliest trial was published in 1991 while the most recent published in 2008.^{114,117} The duration of followup ranged from the postoperative period to 90 days. Two trials received funding from industry,^{114,133} three trials were unfunded,¹¹⁵⁻¹¹⁷ and one trial funding source was not reported.¹³⁴

The mean age of enrolled patients ranged from 64 to years to 69.7 years. Females represented between 55.4 to 67.12 percent of the enrolled populations. The mean weight ranged from 71 to 88 kilograms with only one trial reporting obesity which ranged from 21.43 to 34.38 percent. Few patients enrolled had a history of venous thromboembolism, with the majority of trials reporting 0 to 14 percent. Presence of varicosity was reported as 7 to 46.88 percent. The percent of patients with a history of malignancy ranged from 3.12 to 18.6 percent. None of the trials reported the percent of patients who had previously undergone orthopedic surgery.

Sixty-eight to 100 percent of patients underwent primary surgery and the number of patients who had cemented fixation during surgery ranged from 0 to 100 percent. Mean duration of surgery ranged from 86 to 125 minutes while the mean duration of anesthesia was not reported by any trial. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 12 to 100 percent of patients and regional anesthesia use ranging from 80 to 100 percent of patients. One trial specifically reported use of hypotensive regional anesthesia in all patients.¹¹⁵ The mean length of hospital stay was infrequently reported, and when it was ranged from 3 to 10 days.

Outcome Evaluations

A summary of the results is presented in Table 14.

Symptomatic Objectively Confirmed Venous Thromboembolism

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Major Venous Thromboembolism

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Pulmonary Embolism

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on pulmonary embolism in patients who had major orthopedic surgery.^{114,115} In the trial by Edwards and colleagues in 2008, patients who underwent total hip replacement or total knee replacement were enrolled and the outcomes are included separately for these two populations. All patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. No events occurred in the patients who had total hip replacement surgery and this analysis was not pooled with the others. The patients who had total knee replacement surgery in this study did provide data that could be pooled. In the second trial by Lieberman and colleagues in 1994, patients who had total hip replacement were randomized to receive aspirin plus intermittent pneumatic compression or aspirin alone. All patients also received elastic stockings. In the pooled analysis, in patients who received a combination of pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone the odds of pulmonary embolism were not significantly different [OR 1.03 (0.14 to 7.34)] (Appendix G Figure 211). Statistical heterogeneity and publication bias could not be evaluated because there were too few studies.

Subgroup analyses were not possible in most instances. Limiting the analysis to trials comparing anticoagulant plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the trial by Edwards demonstrated no events in either group in those with total hip replacement and the odds of pulmonary embolism were not significantly different [OR 1.01 (0.06 to 16.35)] in patients who had total knee replacement. This is the same result obtained when limiting the original pooled analysis to trials published from 2001-present. In the trial by Lieberman and colleagues, which compared antiplatelet therapy plus mechanical prophylaxis versus antiplatelet therapy alone, the odds of pulmonary embolism were not significantly different [OR 1.04 (0.06 to 16.82)]. Only the total knee replacement analysis in the Edwards study provided data in that surgery type. In total hip replacement surgery, the evaluation in total hip replacement surgery by Edwards and colleagues had no events, and the study by Lieberman and colleagues found no significant effect. Subgroup analyses based on gender, age and ethnicity were not possible because no data were available.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone on pulmonary embolism in patients who had

major orthopedic surgery.¹¹⁷ This trial by Woolson and colleagues enrolled patients who had total hip replacement and included two comparisons; aspirin plus intermittent pneumatic compression versus intermittent pneumatic compression alone and warfarin plus intermittent pneumatic compression versus intermittent pneumatic compression alone. No events occurred in either the experimental or control group in the warfarin comparison. In patients who received antiplatelet therapy plus intermittent pneumatic compression versus intermittent pneumatic compression alone, the risk of pulmonary embolism was not significantly different [RR 1.57 (0.13 to 19.02)]. Subgroup analyses were possible since this was the only comparison available and data were not available to evaluate the effects of age, gender or ethnicity.

Fatal Pulmonary Embolism

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on fatal pulmonary embolism in patients who had major orthopedic surgery.^{114,115} The comparisons made in these trials included enoxaparin plus intermittent pneumatic compression or enoxaparin alone and aspirin plus intermittent pneumatic compression or aspirin alone. However, no events occurred in the groups compared and therefore the risk of fatal pulmonary embolism could not be calculated.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone in patients who had major orthopedic surgery.

Nonfatal Pulmonary Embolism

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{114,115} The results obtained for all analyses of nonfatal pulmonary embolism are the same as those results and subgroup analyses reported for pulmonary embolism above, as all pulmonary embolism events were nonfatal (Appendix G Figure 212).

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone in patients who had major orthopedic surgery.

Post Thrombotic Syndrome

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Mortality

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on mortality in patients who had major orthopedic surgery although pooling of results was not possible.^{114,115,134} The trial by Stannard and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling because the pharmacologic therapy was sequential in nature; additionally no events occurred in this trial.¹³⁴ In the trial by Edwards and colleagues in 2008, patients who underwent total hip replacement or total knee replacement were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone; however no events occurred in the groups compared.¹¹⁴ The remaining trial by Lieberman and colleagues in 1994 enrolled patients who had total hip replacement and were randomized to receive aspirin plus intermittent pneumatic compression or aspirin alone. In this trial, the odds of mortality were not significantly different in patients who received combination versus single modality prophylaxis [OR 7.72 (0.15 to 389.59)].¹¹⁵ This is the same result obtained when evaluating the impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis on mortality limited to total hip replacement, since the total hip replacement group in the trial by Edwards had no deaths, leaving the trial by Lieberman and colleagues. The one trial by Edwards and colleagues which evaluated total knee replacement did not have any events,¹¹⁴ and no trials evaluated patients who had hip fracture surgery. Subgroup analyses based on gender, age and ethnicity were not possible because no data were available to evaluate the effects of age, gender or ethnicity.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of combined pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone (unfractionated heparin for three days then aspirin plus venous foot pump versus venous foot pump alone) on mortality in patients who had major orthopedic surgery.¹³⁴ No deaths occurred in the groups compared therefore the risk of mortality could not be calculated.

Mortality Due to Bleeding

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on mortality due to bleeding in patients who had major orthopedic surgery.^{114,115,134} The comparisons made in these trials included enoxaparin plus intermittent pneumatic compression or enoxaparin alone, aspirin plus intermittent pneumatic compression or aspirin alone, and unfractionated heparin for three days then aspirin plus venous foot pump versus unfractionated heparin plus aspirin alone. However, no events occurred in the groups compared and therefore the comparative risk of mortality due to bleeding could not be calculated.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

One randomized controlled trial evaluated the impact of combined pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone (unfractionated heparin for three days then aspirin plus venous foot pump versus venous foot pump alone) on mortality due to bleeding in patients who had major orthopedic surgery.¹³⁴ No deaths due to bleeding occurred in the groups therefore the comparative risk of mortality could not be calculated.

Health-Related Quality of Life

No randomized controlled trials or controlled observational trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Deep Vein Thrombosis

Four randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{114,116,133,134} The trial by Stannard and colleagues enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling with the others because the administration of pharmacologic therapy was sequential in nature. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin), the risk of deep vein thrombosis was significantly decreased in patients who received combination prophylaxis versus single modality [RR 0.09 (0.01 to 0.85), NNT 5].

Of the trials amenable for pooling, the trial by Edwards and colleagues enrolled patients who underwent total hip replacement or total knee replacement and reported the results separately for these two populations. Patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. The trial by Kalodiki and colleagues enrolled patients who had total hip replacement surgery and randomized patients to receive either the combination of enoxaparin plus graduated compression stockings or enoxaparin alone. The fourth trial by Westrich and colleagues in 1996 enrolled patients who had total knee replacement surgery and randomized patients to receive either the combination of aspirin plus venous foot pump versus aspirin alone. In this trial, the number of deep vein thromboses was reported out of the number of operated knees because some patients had bilateral surgery while others had unilateral surgery. We only used the unilateral data in pooled analyses. In pooled analysis of the Edwards, Kalodiki, and Westrich trials, patients who received pharmacologic prophylaxis plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of deep vein thrombosis was significantly decreased [RR 0.48 (0.32 to 0.72), NNT 3 to 67] (Appendix G Figure 213).^{114,116,133} Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.637).

When limiting this analysis to only anticoagulant agents combined with mechanical prophylaxis versus an anticoagulant agent alone, the trials by Edwards and Kalodiki and colleagues remained.^{114,133} In patients who received anticoagulant prophylaxis plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.58 (0.32 to 1.06)] (Appendix G Figure 214). Statistical

heterogeneity was not detected ($I^2=0$ percent). In the single trial by Westrich and colleagues which compared antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone, in patients who received the combination versus monotherapy, the risk of deep vein thrombosis was significantly decreased [RR 0.40 (0.23 to 0.68), NNT 3].¹¹⁶

When limiting the original analysis to trials published from 2001-present, the two surgery populations from the trial by Edwards and colleagues remained.¹¹⁴ In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.45 (0.16 to 1.26)] (Appendix G Figure 215). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery, the trials by Edwards and Kalodiki remained.^{114,133} In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone the risk of deep vein thrombosis was not significantly different [RR 0.64 (0.32 to 1.31)] (Appendix G Figure 216). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery the trials by Edwards and Westrich remained.^{114,116} In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone the risk of deep vein thrombosis was significantly decreased [RR 0.41 (0.25 to 0.68), NNT 3 to 18] (Appendix G Figure 217). Statistical heterogeneity could not be evaluated because of too few studies. No trials evaluated patients who had hip fracture surgery and no data were available to evaluate the effects of age, gender or ethnicity.

The trial by Stannard and colleagues also compared pharmacologic prophylaxis plus mechanical prophylaxis versus mechanical prophylaxis alone (unfractionated heparin for three days then aspirin plus venous foot pump versus venous foot pump).¹³⁴ However no events occurred in the groups compared therefore the risk of deep vein thrombosis could not be calculated.

Asymptomatic Deep Vein Thrombosis

One randomized controlled trial by Stannard and colleagues in 1996 evaluated the impact of combination pharmacologic plus mechanical prophylaxis versus single modality prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.¹³⁴ This trial enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone.

In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of asymptomatic deep vein thrombosis was not significantly different in patients who received combination prophylaxis versus single modality [RR 0.20 (0.02 to 2.09)].

In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone, the risk of asymptomatic deep vein thrombosis could not be calculated because no events occurred. Subgroup analyses were not possible since only one trial was available.

Symptomatic Deep Vein Thrombosis

One randomized controlled trial by Stannard and colleagues in 1996 evaluated the impact of combination pharmacologic plus mechanical prophylaxis versus single modality prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.¹³⁴ This trial enrolled patients who had total hip replacement surgery and randomized patients to sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of symptomatic deep vein thrombosis was not significantly different in patients who received combination prophylaxis versus single modality [RR 0.14 (0.01 to 1.42)]. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone, the risk of symptomatic deep vein thrombosis could not be calculated because no events occurred. Subgroup analyses were not possible since only one trial was available.

Proximal Deep Vein Thrombosis

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Five randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.^{114-116,133,134} The first trial by Edwards and colleagues in 2008 enrolled patients who had total hip or total knee replacement and reported the results separately for each surgery.¹¹⁴ Patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. The second trial by Kalodiki and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive either the combination of enoxaparin plus graduated compression stockings or enoxaparin alone; however no events occurred in the groups compared, therefore this trial was excluded from the pooled analysis.¹³³ The third trial by Westrich and colleagues in 1996 enrolled patients who had total knee replacement surgery and randomized patients to receive either the combination of aspirin plus venous foot pump versus aspirin alone.¹¹⁶ The fourth trial by Stannard and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone.¹³⁴ This trial was not suitable for pooling because the sequential nature of the pharmacologic prophylaxis. In this trial, in the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of proximal deep vein thrombosis was significantly decreased in patients who received combination prophylaxis versus single modality [RR 0.09 (0.01 to 0.85), NNT 5]. The fifth trial by Lieberman and colleagues enrolled patients who had total hip replacement surgery and randomized patients to receive aspirin plus intermittent pneumatic compression or aspirin alone.¹¹⁵ All patients also received elastic stockings. This trial was not suitable for pooling because the number of proximal deep vein thromboses was reported out of the total number of hips rather than patients. In this trial, the

odds of proximal deep vein thrombosis were not significantly different in hip surgeries in which patients received combination versus single modality prophylaxis [OR 0.14 (0.003 to 6.93)]. In pooled analysis of the two remaining trials, in patients who received pharmacologic prophylaxis plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.33 (0.09 to 1.22)] (Appendix G Figure 217).^{116,133} Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting this analysis to only anticoagulant agents combined with mechanical prophylaxis versus an anticoagulant agent alone, two trials remained although the trial by Edwards and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving the trial by Kalodiki and colleagues.^{114,133} In this trial, in patients who received anticoagulant prophylaxis plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.44 (0.15 to 1.30)]. In the single trial by Westrich and colleagues which compared antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone, in patients who received the combination versus monotherapy, the risk of proximal deep vein thrombosis was significantly decreased [RR 0.09 (0.01 to 0.84), NNT 8].

Subgroup analysis based on trials published from 2001-present was not possible because only the trial by Edwards and colleagues remained although no events occurred in either surgical population in the groups compared.¹¹⁴ When limiting the original analysis to total hip replacement surgery, two trials remained although the trial by Edwards and colleagues was excluded from the analysis because no events occurred, leaving the trial by Kalodiki and colleagues. In this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.44 (0.15 to 1.30)].¹³³ When limiting the original analysis to total knee replacement surgery, two trials remained although the trial by Edwards and colleagues was excluded because no events occurred in the groups compared, leaving the trial by Westrich and colleagues. In this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.09 (0.01 to 1.51)].¹¹⁶ Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this patient population and data were not reported in a way to evaluate the effects of age, gender or ethnicity.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus mechanical prophylaxis alone.^{117,134} The comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone from the trial by Stannard and colleagues described above was not suitable for pooling because of the sequential nature of the pharmacologic therapy, additionally no events occurred in the groups compared.¹³⁴ The trial by Woolson and colleagues in 1991 enrolled patients who had total hip replacement surgery and randomized patients by hip (not patients since multiple surgeries in the same patient could have been randomized twice to different groups) to receive aspirin plus intermittent pneumatic compression, warfarin plus intermittent pneumatic compression, or intermittent pneumatic compression alone.¹¹⁷ All patients also received graduated compression stockings. In the pooled analysis of the two comparisons in this trial, in hip surgeries in which the patient received pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone, the risk of

proximal deep vein thrombosis was not significantly different [RR 0.78 (0.35 to 1.74)] (Appendix G Figure 218). Statistical heterogeneity and publication bias could not be calculated because of too few studies. This is the same result obtained when limiting the original analysis to total hip replacement because the trial by Stannard and colleagues was ineligible for pooling, leaving the patients from Edwards and colleagues. When evaluating the two comparisons in this trial separately, the risk of proximal deep vein thrombosis was not significantly different in patients who received anticoagulant plus mechanical prophylaxis versus mechanical prophylaxis alone [RR 0.73 (0.28 to 1.88)] or in those who received antiplatelet plus mechanical prophylaxis versus mechanical prophylaxis alone [RR 0.82 (0.33 to 2.02)]. Subgroup analysis based on trial published from 2001-present or limited to total knee replacement or hip fracture surgery was not possible because no trials evaluated this patient population and data were not reported in a way to evaluate the effects of age, gender or ethnicity.

Distal Deep Vein Thrombosis

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on distal deep vein thrombosis in patients who had major orthopedic surgery.^{114,115,134} The first trial by Stannard and colleagues in 1994 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling because the sequential nature of the pharmacologic prophylaxis, additionally no events occurred in the groups compared. The second trial by Lieberman and colleagues in 1994 enrolled patients who had total hip replacement surgery and randomized patients to receive aspirin plus intermittent pneumatic compression or aspirin alone. All patients also received elastic stockings. This trial was not suitable for pooling because the number of distal deep vein thromboses was reported out of the total number of hips rather than patients.¹¹⁵ In this trial, the risk of distal deep vein thrombosis was not significantly different in hip surgeries in which patients received combination versus single modality prophylaxis [RR 0.89 (0.34 to 2.29)]. The third trial by Edwards and colleagues enrolled patients who underwent total hip replacement or total knee replacement and the outcomes are included separately for these two populations. All patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. In the pooled analysis of both groups in the trial by Edwards and colleagues, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis was not significantly different [RR 0.45 (0.16 to 1.26)] (Appendix G Figure 219). This is the same result obtained when pooling trials published from 2001-present or when comparing anticoagulant plus mechanical prophylaxis versus anticoagulant prophylaxis alone. Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the pooled analysis to only patients who had total hip replacement surgery in this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis were not significantly different [RR 0.46 (0.05 to 4.51)].¹¹⁴ When limiting the analysis to only patients who had total knee replacement surgery in this trial, in patients who receive pharmacologic plus mechanical

prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis was not significantly different [RR 0.45 (0.15 to 1.32)].¹¹⁴ Only one trial compared antiplatelet plus mechanical prophylaxis versus mechanical prophylaxis alone.¹¹⁵ In this trial, the risk of distal deep vein thrombosis was not significantly different in hip surgeries in which patients received antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone [RR 0.89 (0.34 to 2.29)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this population no data were available to evaluate the effects of age, gender or ethnicity.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

The trial by Stannard and colleagues also compared pharmacologic prophylaxis plus mechanical prophylaxis versus mechanical prophylaxis alone (unfractionated heparin for three days then aspirin plus venous foot pump or venous foot pump alone).¹³⁴ However no events occurred in the groups compared therefore the risk of distal deep vein thrombosis could not be calculated.

Major Bleeding

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

One randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone (aspirin plus venous foot pump versus aspirin alone) on major bleeding in patients who had major orthopedic surgery however the risk of major bleeding could not be calculated because no events occurred in the groups compared.¹¹⁶ Subgroup analyses were not possible because there was only one trial which evaluated this outcome and no data were available to evaluate the effects of age, gender or ethnicity.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

No randomized controlled trials or observational controlled studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis on this outcome in patients who had major orthopedic surgery.

Major Bleeding Leading to Reoperation

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Minor Bleeding

Pharmacologic Plus Mechanical Versus Pharmacologic Prophylaxis

One randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone (aspirin plus venous foot pump versus aspirin alone) on minor bleeding in patients who had major orthopedic surgery however the risk of major bleeding could not be calculated because no events occurred in the groups compared.¹¹⁶ Subgroup analyses were not possible because there was only one trial which evaluated this outcome and no data were available to evaluate the effects of age, gender or ethnicity.

Pharmacologic Plus Mechanical Versus Mechanical Prophylaxis

No randomized controlled trials or observational controlled studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis on this outcome in patients who had major orthopedic surgery.

Surgical Site Bleeding

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Bleeding Leading to Infection

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Bleeding Leading to Transfusion

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Heparin-Induced Thrombocytopenia

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Discomfort

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Readmission

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Reoperation

No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Strength of Evidence and Applicability of the Body of Evidence

Very few trials compared combination pharmacologic and mechanical prophylaxis versus one of the methods alone, and therefore the majority of outcomes were rated with insufficient strength of evidence in Key Question 7. When comparing pharmacologic plus mechanical to pharmacologic prophylaxis alone, there was moderate strength of evidence that combination therapy decreased the risk of deep vein thrombosis and had no difference on the risk of distal

deep vein thrombosis compared with single modality. There was low strength of evidence that there was no difference in the odds of pulmonary embolism, nonfatal pulmonary embolism, or proximal deep vein thrombosis. When comparing pharmacologic plus mechanical versus mechanical prophylaxis, there was low strength of evidence that there was no difference in the risk of proximal deep vein thrombosis. All other outcomes for both comparisons were rated insufficient.

Overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data. Due to the paucity of available literature, conclusions were sometimes based on a specific combination compared with a single modality in one of the major orthopedic surgeries and therefore the overall applicability of the evidence to combination versus single modality in major orthopedic surgery is limited. In comparing combination prophylaxis to mechanical prophylaxis alone, most comparisons were only in hip replacement surgery.

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?*

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Symptomatic objectively confirmed VTE	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Major VTE	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
PE	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	OR 1.03 (0.14 to 7.34)	NA
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
	• 2001-present	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	• THR	2 RCTs	No	1 RCT had no events; the other showed an OR 1.04 (0.06 to 16.82)	NA
	• TKR	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT (2 comp)	No	1 comparison had no events; the other showed a RR 1.57 (0.13 to 19.02)	NA
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (1 comp)	No	No events occurred in the groups compared	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT (1 comp)	No	RR 1.57 (0.13 to 19.02)	NA
	• THR	1 RCT (2 comp)	No	1 comparison had no events; the other showed a RR 1.57 (0.13 to 19.02)	
Fatal PE	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	No	No events occurred in the groups compared	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Nonfatal PE	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	OR 1.03 (0.14 to 7.34)	NA
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
	• 2001-present	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	• THR	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
	• TKR	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
PTS	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Mortality	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	No	2 RCTs had no events in the groups compared; the third showed an OR of 7.72 (0.15 to 389.50)	NA
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	No	No events occurred in the groups compared	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 7.72 (0.15 to 389.50)	NA
	• 2001-present	1 RCT	No	No events in the groups compared	NA
	• THR	2 RCTs	No	1 RCT had no events; the third showed an OR 7.72 (0.15 to 389.50)	NA
	• TKR	1 RCT	No	No events in the groups compared	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Mortality due to bleeding	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	No	No events occurred in the groups compared	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
HRQOL	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
DVT	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	4 RCTs	Yes	RR 0.48 (0.32 to 0.72)	0
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	Yes	RR 0.58 (0.32 to 1.06)	0
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.40 (0.23 to 0.68)	NA
	• 2001-present	1 RCT (2 comp)	Yes	RR 0.45 (0.16 to 1.26)	NA
	• THR	2 RCTs	Yes	RR 0.64 (0.32 to 1.31)	NA
	• TKR	2 RCTs	Yes	RR 0.41 (0.25 to 0.68)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Asymptomatic DVT	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	RR 0.20 (0.02 to 2.09)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Symptomatic DVT	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	RR 0.14 (0.01 to 1.42)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Proximal DVT	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	Yes	RR 0.33 (0.09 to 1.22)	NA
		2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in 1 trial and RR 0.09 (0.01 to 0.85) in the other trial	
	Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.44 (0.15 to 1.30)	NA
	Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.09 (0.01 to 0.84)	NA
	• 2001-present	1 RCT (2 comp)	No	No events occurred in the groups compared	NA
	• THR	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.44 (0.15 to 1.30)	NA
	• TKR	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.09 (0.01 to 1.51)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	2 RCTs	Yes	RR 0.78 (0.35 to 1.74)	NA
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (1 comp)	No	RR 0.73 (0.28 to 1.88)	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT (1 comp)	No	RR 0.82 (0.33 to 2.02)	NA
	• THR	2 RCTs	Yes	1 RCT was ineligible for pooling; the remaining RCT had 2 comparisons pooled to show a RR 0.78 (0.35 to 1.74)	NA

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Distal DVT	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons which were pooled to show RR 0.45 (0.16 to 1.26)	NA
		1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29)	
	• Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (2 comp)	Yes	RR 0.60 (0.23 to 1.59)	NA
	• Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.89 (0.34 to 2.29)	NA
	• 2001-present	1 RCT (2 comp)	Yes	RR 0.60 (0.23 to 1.59)	NA
	• THR	3 RCTs	Yes	2 RCTs were ineligible for pooling; the remaining RCT had 2 comparisons when pooled showed a RR 0.60 (0.23 to 1.59)	NA
	• TKR	1 RCT	No	RR 0.45 (0.15 to 1.32)	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Major Bleeding	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
Major Bleeding Leading to Reoperation	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Minor Bleeding	Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
	Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---

Table 14. Summary of results for Key Question 7: what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality in patients undergoing major orthopedic surgery?* (continued)

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Surgical Site Bleeding	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Bleeding Leading to Infection	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Bleeding Leading to Transfusion	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
HIT	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Discomfort	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Readmission	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Reoperation	Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---

DVT = deep vein thrombosis; HRQOL = health related quality of life; NA = not applicable; OR = Peto's Odds Ratio; PE = pulmonary embolism; PTS = post thrombotic syndrome; RCT = randomized controlled trial; RR = relative risk; VTE = venous thromboembolism

*All base case analyses are represented in this table. If only one trial was available in a base case analysis no subgroups analyses were performed and therefore are not represented in this table. Only subgroup analyses with trials or studies are represented in this table.

--- No data.

Key Question 8

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7–10 days on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Points

- In this Key Question, the impact of prolonging prophylaxis for 28 days or longer on events was compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery.
- Prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed venous thromboembolism versus shorter term prophylaxis [RR 0.38 (0.19 to 0.77)]. While high heterogeneity was found, the direction of effect was consistent between all of the trials.
 - In subgroup analyses of trials conducted from 2001-present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed venous thromboembolism versus shorter term prophylaxis.
 - In the one trials that stratified results based on gender, women with total hip and total knee replacement surgery had fewer symptomatic venous thromboembolism events after prolonged prophylaxis as did men with total hip replacement.
- Prolonged prophylaxis reduced the occurrence of pulmonary embolism versus shorter term prophylaxis [OR 0.13 (0.04 to 0.47)].
 - In subgroup analyses of trials conducted from 2001-present or in patients undergoing total hip replacement surgery, prolonged prophylaxis reduced the occurrence of pulmonary embolism versus shorter term prophylaxis.
- Prolonged prophylaxis reduced the occurrence of nonfatal pulmonary embolism versus shorter term prophylaxis [OR 0.13 (0.03 to 0.54)].
 - In subgroup analyses of trials conducted from 2001-present or in patients undergoing total hip replacement surgery, prolonged prophylaxis reduced the occurrence of nonfatal pulmonary embolism versus shorter term prophylaxis.
- Prolonged prophylaxis reduced the occurrence of deep venous thrombosis versus shorter term prophylaxis [RR 0.37 (0.21 to 0.64)]. While higher heterogeneity was found, the direction of effect was consistent between all of the trials.
 - In subgroup analyses of trials conducted from 2001-present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis

reduced the occurrence of deep venous thrombosis versus shorter term prophylaxis.

- Prolonged prophylaxis reduced the occurrence of asymptomatic deep venous thrombosis versus shorter term prophylaxis [RR 0.48 (0.31 to 0.75)].
 - In subgroup analyses of patients undergoing total hip replacement surgery, prolonged prophylaxis reduced the occurrence of deep venous thrombosis versus shorter term prophylaxis.
- Prolonged prophylaxis reduced the occurrence of symptomatic deep venous thrombosis versus shorter term prophylaxis [OR 0.36 (0.16 to 0.81)].
- Prolonged prophylaxis reduced the occurrence of proximal deep venous thrombosis versus shorter term prophylaxis [RR 0.29 (0.16 to 0.52)].
 - In subgroup analyses of trials conducted from 2001-present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis reduced the occurrence of proximal deep venous thrombosis versus shorter term prophylaxis.
- While no differences were seen in the base case analysis, prolonged prophylaxis reduced the occurrence of distal deep venous thrombosis versus shorter term prophylaxis in hip fracture surgery.
- Prolonged prophylaxis increases the occurrence of minor bleeding versus shorter term prophylaxis [OR 2.44 (1.44 to 4.20)].
 - In subgroup analyses patients undergoing total hip replacement prolonged prophylaxis increases the occurrence of minor bleeding versus shorter term prophylaxis.
- Prolonged prophylaxis increases the occurrence of surgical site bleeding versus shorter term prophylaxis although this was based on a single randomized controlled trial.
 - In subgroup analyses of trials conducted from 2001-present or patients undergoing hip fracture surgery, prolonged prophylaxis increases the occurrence of surgical site bleeding versus shorter term prophylaxis.
- While no significant difference was seen in the base case analysis, prolonged prophylaxis reduced the occurrence of hospital readmission versus shorter term prophylaxis in total hip replacement surgery.
- Subgroup analyses based on total knee replacement surgery were based on a single comparison from one randomized controlled trial and did not show any statistically significant difference for the outcomes evaluated. These include: symptomatic objectively confirmed venous thromboembolism, pulmonary embolism, nonfatal pulmonary embolism, mortality due to bleeding, overall, proximal, and distal deep vein thrombosis, and major bleeding.

Detailed Analysis

Study Design and Characteristics

Eight randomized controlled trials (N=2,917) and no controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on final, intermediate, or adverse outcomes^{118,121,122,124,126,127,131,198}. All trials were published as full text manuscripts. Six trials (N=1,388) enrolled exclusively patients who had total hip replacement surgery.^{118,122,126,127,131,198} One trial (N=873) enrolled patients who had

either total hip replacement or total knee replacement surgery and reported the results separately for each surgical population.¹²¹ One trial (N=656) enrolled patients who had hip fracture surgery.¹²⁴

One trial (N=656) evaluated the factor Xa inhibitor fondaparinux,¹²⁴ one trial (N=360) evaluated the vitamin K antagonist warfarin,¹³¹ and five trials (N=1,636) evaluated injectable low molecular weight heparin agents including enoxparin and dalteparin.^{118,121,126,127,198} One trial (N=265) compared dalteparin prophylaxis for 7 days versus dalteparin prophylaxis for 35 days but patients also received dextran and graduated compression stockings as part of the randomized prophylaxis regimen therefore this trial was not pooled with other trials and is evaluated separately in this Key Question.¹²² The earliest trial was published in 1997 while the most recent was published in 2003. The duration of followup ranged from 32 to 90 days. Three trials were funded by industry,^{121,124,127} one trial was funded by government/foundation,¹¹⁸ and the remaining trials did not disclose the funding source.

The mean age of enrolled patients ranged from 63.4 years to 79 years. Females represented between 38.2 and 73.6 percent of the enrolled populations. The mean weight ranged from 65 to 89.2 kilograms and obesity ranged from 7.8 to 75.1 percent. Few patients enrolled had a history of venous thromboembolism ranging from 1.12 to 9.0 percent. Presence of varicosity ranged from 7.6 to 24 percent. The percent of patients with a history of malignancy ranged from 1.7 to 9.4 percent. Few trials reported the percent of patients who had previously undergone orthopedic surgery ranging from 3.6 to 13.33 percent.

Seventy-two to 100 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 23.9 to 84.1 percent. Mean duration of surgery ranged from 95 to 114 minutes and the mean duration of anesthesia was reported by two trials with a range of 125.83 to 165 minutes. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 0.88 to 97.2 percent of patients and regional anesthesia use ranging from 25.0 to 99.12 percent of patients. The mean length of hospital stay was reported by one trial, and it was 9 days.

Outcome Evaluations

A summary of the results is presented in Table 15.

Symptomatic Objectively Confirmed Venous Thromboembolism

Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.^{121,124,126,131} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement surgery).¹²¹ In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.38 (0.19 to 0.77), NNT 8 to 54] (Appendix G Figure 220). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=69.1$ percent, Egger's p-value=0.150). The direction of effect was the same in all of the trials and differed only in the magnitude of the effect. Some of the heterogeneity may be related to the type of surgery.

When limiting the original analysis to trials published from 2001-present three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.^{121,124,131} In patients who received prolonged prophylaxis versus standard duration

prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.43 (0.20 to 0.89), NNT 8 to 59] (Appendix G Figure 221). A higher level of statistical heterogeneity was detected ($I^2=72.9$ percent). When limiting the original analysis to total hip replacement surgery three trials remained.^{121,126,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.33 (0.21 to 0.51), NNT 7 to 30] (Appendix G Figure 222). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was not significantly different [RR 0.84 (0.57 to 1.23)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.11 (0.02 to 0.68), NNT 38].

The trial by Comp and colleagues evaluated the impact of gender on the efficacy of extended duration prophylaxis versus standard duration prophylaxis on symptomatic venous thromboembolism in patients who had major orthopedic surgery.¹²¹ Two surgical populations were evaluated separately in this trial; total hip replacement and total knee replacement surgery. In males, extended duration prophylaxis significantly reduced the percent of patients who had symptomatic venous thromboembolism compared with standard duration prophylaxis in patients who had total hip replacement (6.3 percent versus 23.6, $p < 0.001$) but not in those who had total knee replacement (23.6 percent versus 15.3 percent, $p=0.211$). In females extended duration prophylaxis significantly reduced the percent of patients who had symptomatic venous thromboembolism compared with standard duration prophylaxis in patients who had total hip replacement (9.7 percent versus 22.9, $p=0.014$) and in those who had total knee replacement (13.3 percent versus 25.2 percent, $p=0.025$).

Major Venous Thromboembolism

One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on major venous thromboembolism in patients who had major orthopedic surgery.¹³¹ This trial by Prandoni and colleagues in 2002 evaluated patients who had total hip replacement surgery and received warfarin prophylaxis for 28 days versus warfarin prophylaxis until hospital discharge, with a mean hospital length of stay of 9 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major venous thromboembolism were not significantly different [OR 0.34 (0.11 to 1.07)]. Subgroup analyses were not possible as only one trial with events was available.

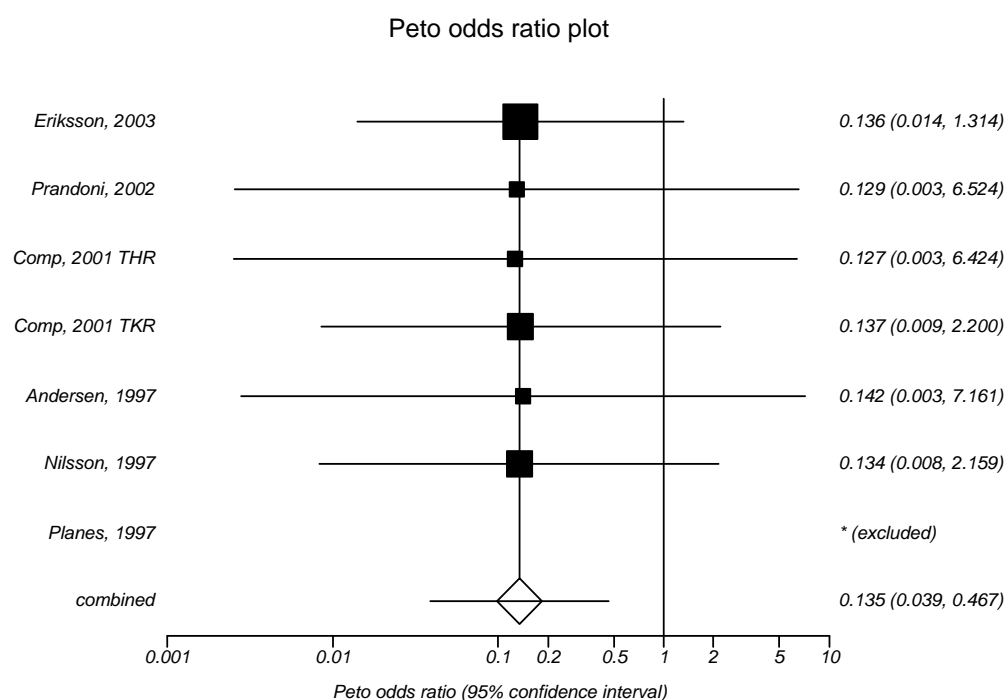
Pulmonary Embolism

Seven randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on pulmonary embolism in patients who had major orthopedic surgery.^{118,121,122,124,126,127,131} The trial by Comp and colleagues included two separate comparisons based on the surgery type; total hip replacement and total knee replacement surgery and the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.^{121,127} The trial by Dahl and colleagues was

evaluated separately from the pooled analysis because patients received triple prophylaxis.¹²² The remaining five trials were pooled and in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.14 (0.04 to 0.47), NNT 24 to 232] (Figure 11). Statistical heterogeneity and publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.471).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.54 (0.16 to 1.80)].

Figure 11. Impact of prolonged prophylaxis versus standard duration of prophylaxis on pulmonary embolism in patients who had major orthopedic surgery



I^2 : 0 percent.

Egger's p -value: 0.471.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

When limiting the original analysis to trials published from 2001-present three trials remained, with the trial by Comp and colleagues including two separate comparisons based on surgery type.^{121,124,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.59), NNT 9 to 232] (Appendix G Figure 223). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement surgery five trials remained although the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.^{118,121,126,127,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly

decreased [OR 0.13 (0.02 to 0.77), NNT 24] (Appendix G Figure 224). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.20)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.14 (0.01 to 1.31)].

Fatal Pulmonary Embolism

Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on fatal pulmonary embolism in patients who had major orthopedic surgery.^{121,122,124,126,127,131} Four trials were excluded from the analysis because no events occurred. The trial by Dahl and colleagues was evaluated separately because patients received triple prophylactic therapy.¹²² The remaining trial by Eriksson and colleagues in 2003 evaluated patients who had hip fracture surgery and who received fondaparinux prophylaxis for 25 to 31 days versus fondaparinux prophylaxis for 6 to 8 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.90)]. Subgroup analyses were not possible as only one trial with events was available.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial the odds of fatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.51)] in patients who received prolonged prophylaxis versus shorter duration prophylaxis.

Nonfatal Pulmonary Embolism

Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on nonfatal pulmonary embolism in patients who had major orthopedic surgery.^{121,122,124,126,127,131} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement surgery) and the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.^{121,127} The trial by Dahl and colleagues was evaluated separately from the pooled analysis because patients received triple prophylactic therapy.¹²² The four remaining trials were pooled and in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.54), NNT 58] (Appendix G Figure 225). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected although the presence of publication bias was detected ($I^2=0$ percent, Egger's p -value=0.016). The directionality of the publication bias, however, was unclear.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial the

odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.06)] in patients who received prolonged prophylaxis versus shorter duration prophylaxis.

When limiting the original analysis to trials published from 2001-present, three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.^{121,124,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.66), NNT 9 to 232] (Appendix G Figure 226). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total hip replacement surgery four trials remained although the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.^{121,126,127,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.02 to 0.93), NNT 58] (Appendix G Figure 227). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.20)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.19)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

Post thrombotic Syndrome

No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Mortality

Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on mortality in patients who had major orthopedic surgery.^{121,122,124,126,127,131} The trial by Dahl and colleagues was evaluated separately because patients received triple prophylactic therapy.¹²² Four trials were excluded from the analysis because no events occurred, leaving the trial by Eriksson and colleagues in 2003. This trial evaluated patients who had hip fracture surgery and received fondaparinux prophylaxis for 25 to 31 days versus fondaparinux prophylaxis for 6 to 8 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of mortality were not significantly different [OR 0.75 (0.26 to 2.17)]. Subgroup analyses were not possible as only one trial with events was available.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial the risk of mortality was not significantly different [RR 0.98 (0.10 to 9.31)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

Mortality Due to Bleeding

Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on mortality due to bleeding in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality due to bleeding could not be calculated.^{121,122,126,127,131}

Health Related Quality of Life

No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Deep Vein Thrombosis

Eight randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on deep vein thrombosis in patients who had major orthopedic surgery.^{118,121,122,124,126,127,131,198} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).¹²¹ The trial by Dahl and colleagues was evaluated separately from the analysis because patients received triple prophylactic therapy.¹²² In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.37 (0.21 to 0.64), NNT 5 to 32] (Appendix G Figure 228). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected ($I^2=78.3$ percent, Egger's p-value=0.164).

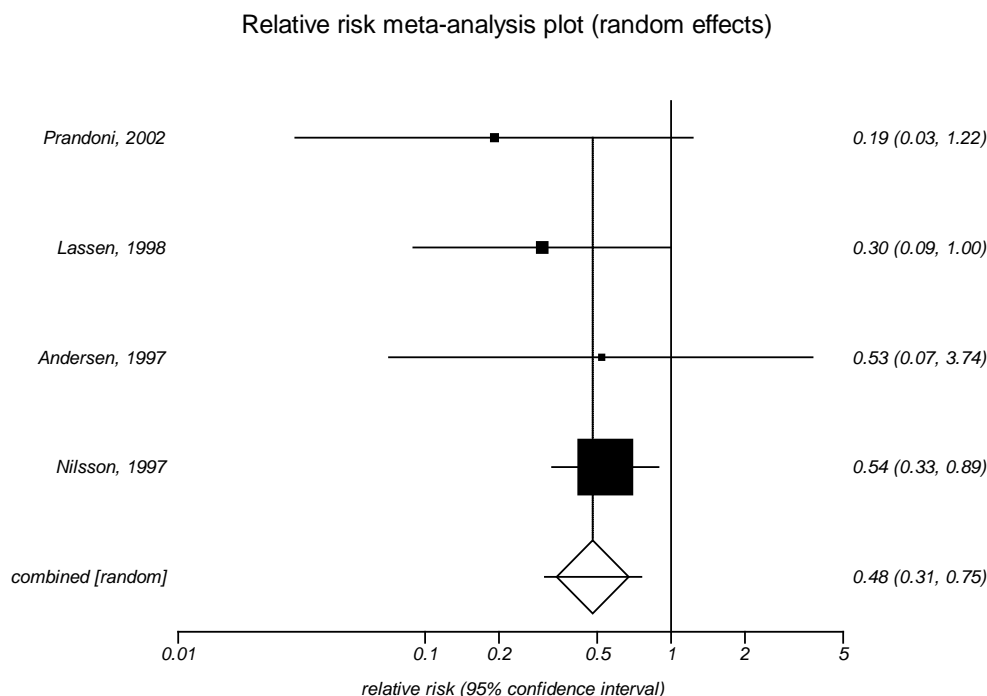
The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.61 (0.38 to 0.97)].

When limiting the original analysis to trials published from 2001-present three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.^{121,124,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.28 (0.09 to 0.87), NNT 5 to 28] (Appendix G Figure 229). A higher level of statistical heterogeneity was detected ($I^2=90.9$ percent). When limiting the original analysis to total hip replacement surgery six trials remained.^{118,121,126,127,131,198} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.41 (0.31 to 0.55), NNT 6 to 34] (Appendix G Figure 230). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was not significantly different [RR 0.84 (0.57 to 1.23)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.04 (0.01 to 0.12), NNT 4].

Asymptomatic Deep Vein Thrombosis

Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{118,126,131,198} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of asymptomatic deep venous thrombosis was significantly decreased [RR 0.48 (0.31 to 0.75), NNT 8 to 65] (Figure 12). Statistical heterogeneity and the presence of publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.252). This is the same result obtained when limiting the analysis to total hip replacement surgery since all four trials evaluated this surgical population. When limiting the original analysis to trials published from 2001-present, one trial remained.¹³¹ In this trial, the odds of asymptomatic deep vein thrombosis were not significantly different [OR 0.25 (0.05 to 1.24)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. Subgroup analysis based on total knee replacement or hip fracture surgery were not possible since no trials evaluated these surgical populations.

Figure 12. Impact of prolonged prophylaxis versus standard duration of prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery (same as limited to total hip replacement surgery)



I^2 : 0 percent.

Egger's p -value: 0.252.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

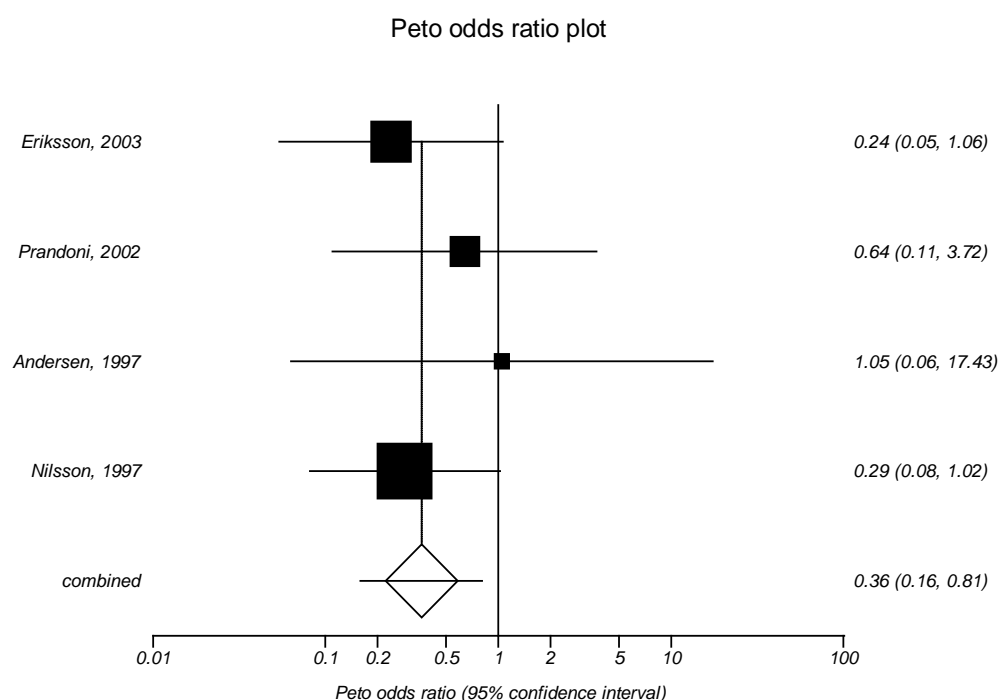
Symptomatic Deep Vein Thrombosis

Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.^{118,122,124,126,131} The trial by Dahl and colleagues was

evaluated separately because patients received triple prophylactic therapy.¹²² In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were significantly decreased [OR 0.36 (0.16 to 0.81), NNT 27 to 79] (Figure 13). Statistical heterogeneity and the presence of publication bias were not detected ($I^2=0$ percent, Egger's p -value=0.155).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.83 (0.57 to 5.87)].

Figure 13. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 0 percent.

Egger's p -value: 0.155.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

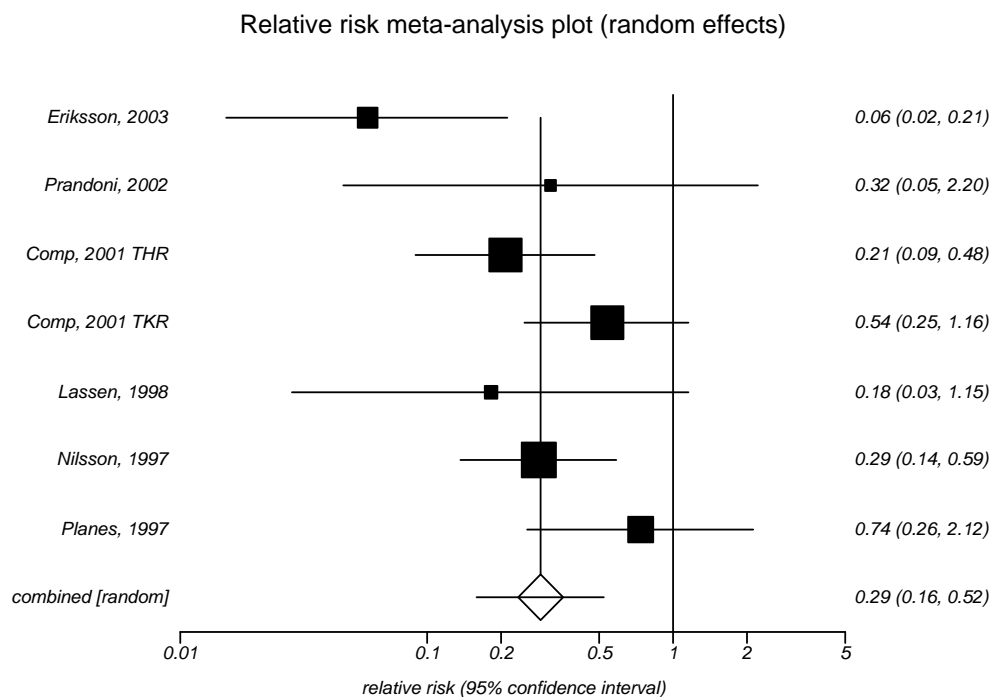
When limiting the original analysis to trials published from 2001-present, two trials remained.^{124,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.36 (0.12 to 1.12)] (Appendix G Figure 231). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery three trials remained.^{118,126,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.43 (0.16 to 1.12)] (Appendix G Figure 232). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to hip fracture surgery one trial

remained.¹²⁴ In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.24 (0.05 to 1.06)]. Subgroup analysis based on total knee replacement surgery was not possible as no trials evaluated this surgical population.

Proximal Deep Vein Thrombosis

Seven randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on proximal deep vein thrombosis in patients who had major orthopedic surgery.^{121,122,124,126,127,131,198} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).¹²¹ The trial by Dahl and colleagues was evaluated separately from the analysis because patients received triple prophylactic therapy.¹²² In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.29 (0.16 to 0.52), NNT 9 to 71] (Figure 14). A lower level of statistical heterogeneity was detected and the presence of publication bias was not detected ($I^2=48.1$ percent, Egger's p-value=0.507).

Figure 14. Impact of prolonged prophylaxis versus standard duration of prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 48.1 percent.

Egger's p-value: 0.507.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.¹²² In this trial the

risk of proximal deep vein thrombosis was not significantly different [RR 0.65 (0.31 to 1.38)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

When limiting the original analysis to trials published from 2001-present, three trials remained.^{121,124,131} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.23 (0.08 to 0.61), NNT 8 to 57] (Appendix G Figure 233). A higher level of statistical heterogeneity was detected ($I^2=65.5$ percent). When limiting the original analysis to total hip replacement surgery five trials remained.^{121,126,127,131,198} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.30 (0.19 to 0.49), NNT 7 to 72] (Appendix G Figure 234). Statistical heterogeneity was not detected ($I^2=0$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.54 (0.25 to 1.16)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.06 (0.02 to 0.21), NNT 7].

Distal Deep Vein Thrombosis

Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on distal deep vein thrombosis in patients who had major orthopedic surgery.^{121,124,126,127} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).¹²¹ In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.39 (0.15 to 1.04)] (Appendix G Figure 235). A higher statistical heterogeneity was detected as was the presence of publication bias ($I^2=83.6$ percent, Egger's p -value=0.023). Publication bias suggests that larger trials with decreased risk and smaller trials with increased risk of distal deep vein thrombosis were omitted.

When limiting the original analysis to trials published from 2001-present, two trials remained with the trial by Comp and colleagues contributing two separate comparisons.^{121,124} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.33 (0.07 to 1.51)] (Appendix G Figure 236). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery three trials remained.^{121,126,127} In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.53 (0.24 to 1.17)] (Appendix G Figure 237). A higher level of statistical heterogeneity was detected ($I^2=53.4$ percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 1.09 (0.67 to 1.78)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.02 (0.004 to 0.14), NNT 6].

Major Bleeding

Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on major bleeding in patients who had major orthopedic surgery.^{121,124,127,131,198} The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).¹²¹ One trial and one comparison in total hip replacement surgery by Comp and colleagues were excluded from the analysis because no events occurred in the groups compared.^{121,127} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 2.18 (0.73 to 6.51)] (Appendix G Figure 238). A lower statistical heterogeneity was detected and the presence of publication bias was not detected ($I^2=35.6$ percent, Egger's p -value=0.334).

When limiting the original analysis to trials published from 2001-present, three trials remained with the trial by Comp and colleagues contributing two separate comparisons.^{121,124,131} The comparison in total hip replacement surgery by Comp and colleagues was excluded from the analysis because no events occurred in the groups compared. In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 2.76 (0.88 to 8.61)] (Appendix G Figure 239). A lower level of statistical heterogeneity was detected ($I^2=22.3$ percent). When limiting the original analysis to total hip replacement surgery four trials remained.^{121,127,131,198} Two trials were excluded from the analysis because no events occurred in the groups compared.^{121,127} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 0.98 (0.06 to 15.70)] (Appendix G Figure 240). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.¹²¹ In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 0.14 (0.003 to 6.95)]. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 3.40 (0.98 to 11.84)].

Major Bleeding Leading to Reoperation

One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on major bleeding leading to reoperation in patients who had major orthopedic surgery.¹²⁴ In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 1.01 (0.14 to 7.18)]. Subgroup analysis was not possible because there was only one study available.

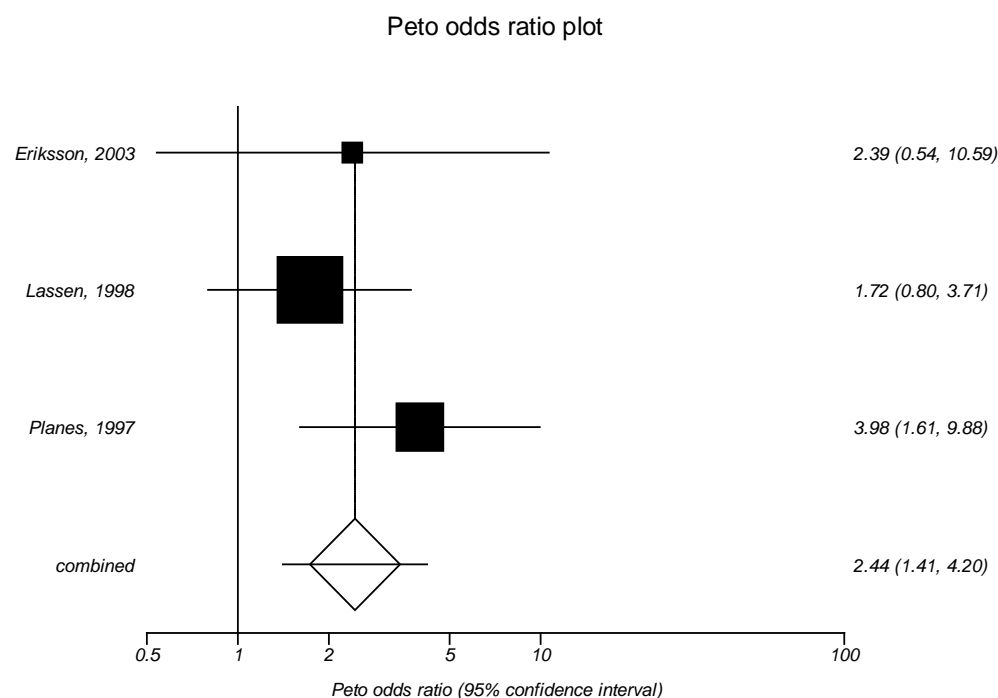
Minor Bleeding

Three randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on minor bleeding in patients who had major orthopedic surgery.^{124,127,198} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were significantly increased [OR 2.44

(1.41 to 4.20), NNH 11 to 118] (Figure 15). Statistical heterogeneity was not detected while publication bias not could be evaluated because of too few studies ($I^2=0$ percent).

When limiting the original analysis to trials published from 2001-present, one trial remained.¹²⁴ In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were not significantly different [OR 2.39 (0.54 to 10.59)]. When limiting the original analysis to total hip replacement surgery two trials remained.^{127,198} In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were significantly increased [OR 2.44 (1.36 to 4.39), NNH 11 to 20] (Appendix G Figure 241). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on total knee replacement surgery could not be evaluated because no trials evaluated this surgical population. When limiting the original analysis to hip fracture surgery one trial remained.¹²⁴ In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were not significantly different [OR 2.39 (0.54 to 10.59)].

Figure 15. Impact of prolonged prophylaxis versus standard duration of prophylaxis on minor bleeding in patients who had major orthopedic surgery



I^2 : 0 percent.

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Surgical Site Bleeding

One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on surgical site bleeding in patients who had major orthopedic surgery.¹²⁴ In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In patients who received

prolonged prophylaxis versus standard duration prophylaxis the odds of surgical site bleeding were significantly increased [OR 7.55 (1.51 to 37.64)]. The number needed to harm could not be calculated because the control event rate was zero. Subgroup analysis was not possible because there was only one study available.

Bleeding Leading to Infection

No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Bleeding Leading to Transfusion

Two randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on bleeding leading to transfusion in patients who had major orthopedic surgery.^{124,127} One trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving one trial for the analysis. In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In this trial, the risk of bleeding leading to transfusion was not significantly different [RR 1.46 (0.85 to 2.51)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. Subgroup analyses were not possible since only one trial with events was available.

Heparin-Induced Thrombocytopenia

No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Discomfort

No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Readmission

One randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on readmission in patients who had major orthopedic surgery.¹²¹ This trial by Comp and colleagues in 2001 included two separate comparisons based on the surgery type (total hip replacement and total knee replacement). When pooling these two comparisons, in patients who had major orthopedic surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of readmission was not significantly different [RR 0.29 (0.06 to 1.34)] (Appendix G Figure 242). Patients were randomized to receive enoxaparin prophylaxis for 7 to 10 days versus enoxaparin prophylaxis for 28 to 31 days. In patients who had total hip replacement surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of readmission was significantly decreased [RR 0.13 (0.04 to 0.39), NNT 12 to 23]. In patients who had total knee replacement surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of

readmission was not significantly different [RR 0.59 (0.24 to 1.44)]. Subgroup analyses based on hip fracture surgery was not possible since no trials evaluated this surgical population.

Reoperation

One randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared with prophylaxis for 7 to 10 days on reoperation in patients who had major orthopedic surgery.¹¹⁸ This trial by Andersen and colleagues in 1997 evaluated patients who had total hip replacement surgery and received dalteparin prophylaxis for 5 to 7 days versus dalteparin prophylaxis for 35 days. In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of reoperation was not significantly different [RR 0.21 (0.02 to 2.16)]. Subgroup analyses were not possible as only one trial was available.

Strength of Evidence and Applicability of the Body of Evidence

Relative to other Key Questions evaluating prophylaxis in major orthopedic surgery, Key Question 8 had the highest overall strength of evidence for outcomes evaluated. Overall there is a better comparative balance of benefits to harms for prolonging prophylaxis. There was high strength of evidence that prolonged prophylaxis decreased the risk of pulmonary embolism, asymptomatic or symptomatic or proximal deep vein thrombosis, moderate strength of evidence that prolonged prophylaxis decreased the risk of symptomatic objectively confirmed venous thromboembolism, deep vein thrombosis, and the odds of nonfatal pulmonary embolism. There was low strength of evidence that there was no difference in the risk of distal deep vein thrombosis, readmission or odds of major bleeding. The one harm which had high strength of evidence was the risk of minor bleeding, which was increased with prolonged prophylaxis. Other outcomes were rated as insufficient.

Overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data. The main limitation to the overall applicability was the lack of variety of pharmacologic classes evaluated. Almost all trials compared shorter versus longer term use of low molecular weight heparins and therefore, the applicability to other classes is limited. Often the majority of trials were conducted outside of the United States.

Table 15. Summary of results for Key Question 8: regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7-10 days in patients undergoing major orthopedic surgery*

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Symptomatic objectively confirmed VTE	Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.38 (0.19 to 0.77)	69.1
	• 2001-present	3 RCTs	Yes	RR 0.43 (0.20 to 0.89)	72.9
	• THR	3 RCTs	Yes	RR 0.33 (0.21 to 0.51)	0
	• TKR	1 RCT (1 comp)	No	RR 0.84 (0.57 to 1.23)	NA
	• HFS	1 RCT	No	RR 0.11 (0.02 to 0.68)	NA
	• Age, gender, ethnicity	1 RCT	No	RCT showed that extended duration prophylaxis significantly reduced the percent of patients with symptomatic venous thromboembolism in males and in females undergoing THR and in females undergoing TKR. In males undergoing TKR, there was no significant difference in the percent of patients with symptomatic venous thromboembolism	NA
Major VTE	Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 0.34 (0.11 to 1.07)	NA
PE	Prolonged prophylaxis versus standard duration prophylaxis	6 RCTs	Yes	OR 0.14 (0.04 to 0.47)	0
		1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80)	NA
	• 2001-present	3 RCTs	Yes	OR 0.13 (0.03 to 0.59)	0
	• THR	5 RCTs	Yes	OR 0.13 (0.02 to 0.77)	0
	• TKR	1 RCT (1 comp)	No	OR 0.14 (0.01 to 2.20)	NA
	• HFS	1 RCT	No	OR 0.14 (0.01 to 1.31)	NA
Fatal PE	Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	Four trials had no events; remaining trial showed OR 0.14 (0.003 to 6.90)	NA
		1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.003 to 6.51)	NA
	• 2001-present	3 RCTs	No	Two trials had no events; remaining trial showed OR 0.14 (0.003 to 6.90)	NA
	• THR	5 RCTs	No	Four trials had no events; one trial ineligible for pooling showed OR 0.13 (0.003 to 6.51)	NA
	• HFS	1 RCT	No	OR 0.14 (0.003 to 6.90)	NA
Nonfatal PE	Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	OR 0.13 (0.03 to 0.54)	0

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
		1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)	NA
	• 2001-present	3 RCTs	Yes	OR 0.13 (0.03 to 0.66)	0
	• THR	4 RCTs	Yes	OR 0.13 (0.02 to 0.93)	0
		1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)	NA
	• TKR	1 RCT (1 comp)	No	OR 0.14 (0.01 to 2.20)	NA
	• HFS	1 RCT	No	OR 0.14 (0.01 to 2.19)	NA
PTS	Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Mortality	Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	No	Four trials had no events; remaining trial showed OR 0.75 (0.26 to 2.17)	NA
		1 RCT	No	One trial ineligible for pooling showed RR 0.98 (0.10 to 9.31)	NA
	• 2001-present	3 RCTs	No	2 trials were excluded from the analysis because no events occurred in the groups compared; remaining trial showed OR 0.75 (0.26 to 2.17)	NA
	• THR	4 RCTs	No	3 trials were excluded from the analysis because no events occurred in the groups compared; one trial ineligible for pooling showed RR 0.98 (0.10 to 9.31)	NA
	• TKR	1 RCT	No	No events occurred in the groups compared	NA
	• HFS	1 RCT	No	OR 0.75 (0.26 to 2.17)	NA
Mortality due to bleeding	Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	No	No events occurred in the groups compared	NA
	• 2001-present	2 RCTs	No	No events occurred in the groups compared	NA
	• THR	5 RCTs	No	No events occurred in the groups compared	NA
	• TKR	1 RCT	No	No events occurred in the groups compared	NA
HRQOL	Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
DVT	Prolonged prophylaxis versus standard duration prophylaxis	7 RCTs	Yes	RR 0.37 (0.21 to 0.64)	78.3
		1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)	NA
	• 2001-present	3 RCTs	Yes	RR 0.28 (0.09 to 0.87)	90.9
	• THR	6 RCTs	Yes	RR 0.41 (0.31 to 0.55)	0
		1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)	NA
	• TKR	1 RCT	No	RR 0.84 (0.57 to 1.23)	NA
	• HFS	1 RCT	No	RR 0.04 (0.01 to 0.12)	NA

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Asymptomatic DVT	Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.48 (0.31 to 0.75)	0
	• 2001-present	1 RCT	No	OR 0.25 (0.05 to 1.24)	NA
	• THR	4 RCTs	Yes	RR 0.48 (0.31 to 0.75)	0
Symptomatic DVT	Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	OR 0.36 (0.16 to 0.81)	0
		1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)	NA
	• 2001-present	2 RCTs	Yes	OR 0.36 (0.12 to 1.12)	NA
		4 RCTs	Yes	OR 0.43 (0.16 to 1.12)	0
	• THR	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)	NA
	• HFS	1 RCT	No	OR 0.24 (0.05 to 1.06)	NA
Proximal DVT	Prolonged prophylaxis versus standard duration prophylaxis	6 RCTs	Yes	RR 0.29 (0.16 to 0.52)	48.1
		1 RCT		One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)	NA
	• 2001-present	3 RCTs	Yes	RR 0.23 (0.08 to 0.61)	65.5
		5 RCTs	Yes	RR 0.30 (0.19 to 0.49)	0
	• THR	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)	NA
	• TKR	1 RCT (1 comp)	No	RR 0.54 (0.25 to 1.16)	NA
	• HFS	1 RCT	No	RR 0.06 (0.02 to 0.21)	NA
Distal DVT	Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.39 (0.15 to 1.04)	83.6
	• 2001-present	2 RCTs	Yes	RR 0.33 (0.07 to 1.51)	NA
	• THR	3 RCTs	Yes	RR 0.53 (0.24 to 1.17)	53.4
	• TKR	1 RCT (1 comp)	No	RR 1.09 (0.67 to 1.78)	NA
	• HFS	1 RCT	No	RR 0.02 (0.004 to 0.14)	NA
Major bleeding	Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	OR 2.18 (0.73 to 6.51)	35.6
	• 2001-present	3 RCTs	Yes	OR 2.76 (0.88 to 8.61)	22.3
	• THR	2 RCTs	Yes	OR 0.98 (0.06 to 15.70)	NA
	• TKR	1 RCT (1 comp)	No	OR 0.14 (0.003 to 6.95)	NA
	• HFS	1 RCT	No	OR 3.40 (0.98 to 11.84)	NA
Major bleeding leading to reoperation	Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 1.01 (0.14 to 7.18)	NA

	Endpoint/Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I ² (%)
Minor bleeding	Prolonged prophylaxis versus standard duration prophylaxis	3 RCTs	Yes	OR 2.44 (1.41 to 4.20)	0
	• 2001-present	1 RCT	No	OR 2.39 (0.54 to 10.59)	NA
	• THR	2 RCTs	Yes	OR 2.44 (1.36 to 4.39)	NA
	• HFS	1 RCT	No	OR 2.39 (0.54 to 10.59)	---
Surgical site bleeding	Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 7.55 (1.51 to 37.64)	NA
Bleeding leading to infection	Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Bleeding leading to transfusion	Prolonged prophylaxis versus standard duration prophylaxis	2 RCTs	No	1 trial was excluded from the analysis because no events occurred in the groups compared; remaining trial showed RR 1.46 (0.85 to 2.51)	NA
	• 2001-present	2 RCTs	No	1 trial was excluded from the analysis because no events occurred in the groups compared; remaining trial showed RR 1.46 (0.85 to 2.51)	NA
	• THR	1 RCT	No	No events occurred in the groups compared	NA
	• HFS	1 RCT	No	RR 1.46 (0.85 to 2.51)	NA
HIT	Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Discomfort	Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Readmission	Prolonged prophylaxis versus standard duration prophylaxis	1 RCT (2 comp)	Yes	RR 0.29 (0.96 to 1.34)	NA
	• 2001-present	1 RCT (2 comp)	Yes	RR 0.29 (0.96 to 1.34)	NA
	• THR	1 RCT (1 comp)	No	RR 0.13 (0.04 to 0.39)	NA
	• TKR	1 RCT (1 comp)	No	RR 0.59 (0.24 to 1.44)	NA
Reoperation	Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	RR 0.21 (0.02 to 2.16)	NA

DVT = deep vein thrombosis; HFS = hip fracture surgery; HIT = heparin induced thrombocytopenia; LMWH = low molecular weight heparin; NA = not applicable; OR = Peto's Odds Ratio; PE = pulmonary embolism; PTS = post thrombotic syndrome; RCT = randomized controlled trial; RR = relative risk; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin; VKA = vitamin K antagonist

*All base case analyses are represented in the table. Subgroup analyses without available data are not represented in this table. If only 1 trial was available subgroup analyses were not run.

--- No data.

Key Question 9

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter placement compared with any external mechanical intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, reoperation, and inferior vena cava filter placement associated insertion site thrombosis?

No randomized controlled trials or controlled observational studies met our inclusion criteria for this Key Question and therefore all outcomes were rated as insufficient strength of evidence.

Key Question 10

In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation?

Key Points

- There is a relative paucity of data comparing prophylactic strategies to no prophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery.
 - No randomized controlled trial or controlled observational studies evaluating elective spine surgery met inclusion criteria.
 - One trial evaluated the injectable low molecular weight heparin dalteparin versus placebo for 6 weeks in patients who had Achilles tendon rupture surgery. There were no significant differences in the occurrence of deep vein thrombosis or proximal deep vein thrombosis at 6 weeks. No patients presented with clinical pulmonary emboli or had episodes of major bleeding.
 - One trial evaluated the injectable low molecular weight heparin dalteparin versus control for up to 30 days in patients who had arthroscopic knee surgery.

Significantly fewer patients who received dalteparin developed a deep vein thrombosis or distal deep vein thrombosis. None of the deep vein thromboses were proximal. One patient in the dalteparin group developed a pulmonary embolism and also had a deep vein thrombosis. No patients had major bleeding and the occurrence of minor bleeding was not significantly different between the two groups.

Detailed Analysis

Study Design and Characteristics

Two randomized controlled trials (N=235) and no controlled observational studies evaluated the impact of prophylaxis versus no prophylaxis on final, intermediate, or adverse health outcomes.^{191,192} The first trial by Lapidus and colleagues in 2007 enrolled patients who had Achilles tendon rupture surgery and randomized patients to receive the injectable low molecular weight heparin dalteparin versus placebo injections for 6 weeks.¹⁹² This trial was published as a full text manuscript and was funded by industry and government/foundation. The mean age of enrolled patients ranged from 37 to 42 years and females represented 21 percent of the enrolled population. The mean weight ranged from 80 to 81 kilograms; obesity was not reported. None of the patients had a history of venous thromboembolism and 5.8 to 11.3 percent of patients had the presence of varicosity. The history of malignancy or prior orthopedic surgery was not reported. The mean duration of surgery ranged from 44 to 45 minutes and 100 percent of participants received regional anesthesia. Tourniquet use was reported in 11.3 to 11.5 percent of patients. As this was an outpatient procedure patients were not hospitalized.

The second trial by Michot and colleagues in 2002 enrolled patients who had diagnostic or therapeutic arthroscopic knee surgery and were randomized to receive the injectable low molecular weight heparin dalteparin versus control for 30 days.¹⁹¹ Diagnostic procedures were performed in 17 to 18 percent of patients while the majority of patients underwent therapeutic procedures (73 percent). Of the therapeutic procedures included, partial meniscectomy represented the majority of procedures (73.4 to 79.2 percent). The trial was published as a full text manuscript and the funding source was not disclosed. The mean age of enrolled patients ranged from 42.0 to 46.5 years and females represented 28.1 to 39.4 percent of the enrolled population. Mean body mass index was reported and ranged from 26.2 to 27.8 kilograms per meter squared. The presence of varicosity was reported in 12.1 to 14.1 percent of patients. The use of general anesthesia ranged from 29.7 to 33.3 percent, regional anesthesia ranged from 66.7 to 70.3 percent, and the use of both types of anesthesia ranged from 3.0 to 3.1 percent of the enrolled population. No other surgical characteristics were reported. As this was an outpatient procedure patients were not hospitalized.

Outcome Evaluations

Achilles Tendon Rupture Surgery

One trial by Lapidus and colleagues enrolled 105 patients who had Achilles tendon rupture surgery and randomized patients to receive dalteparin 5,000 units subcutaneously every day (n=52) or placebo saline injections daily (n=53) for six weeks.¹⁹² After surgery, a below-knee plaster cast was applied in all patients and was replaced by another plaster cast or orthosis at three weeks at which time full weight bearing was allowed. Followup visits were scheduled at

three and six weeks at which time patients were screened clinically for signs and symptoms of deep vein thrombosis and pulmonary embolism and underwent unilateral color duplex sonography. Venography was used to confirm cases of deep vein thrombosis identified with sonography or when sonography was inconclusive.

In this trial, in patients who received dalteparin prophylaxis versus placebo, the risk of deep vein thrombosis (distal or proximal) was not significantly different at the sixth postoperative week (36.7 percent versus 40.4 percent, $p=0.80$). The same result was seen when evaluating proximal deep vein thrombosis (2.0 percent versus 6.4 percent, $p=0.60$). No patients presented with clinical signs or symptoms of pulmonary embolism during the followup period and no patients had major bleeding which was defined as bleeding requiring blood transfusion or into a critical organ (intraocular, intracranial, intraspinal or retroperitoneal).

Knee Arthroscopy

One trial by Michot and colleagues enrolled 130 patients who had diagnostic or therapeutic arthroscopic knee surgery and randomized patients to receive dalteparin subcutaneous injections daily ($n=66$) versus control ($n=64$) up to 30 days postoperatively.¹⁹¹ All patients received dalteparin 2,500 units 60 to 120 minutes prior to the start of surgery and subsequent dosing was weight based; 2500 units daily if weighing less than or equal to 70 kilograms and 5,000 units daily if weighing greater than 70 kilogram. Concomitant therapy with antiplatelet or anticoagulant therapy was not permitted. Patients were instructed to bear weight immediately after the surgery or as tolerated on crutches for 24 to 48 hours. Followup visits were scheduled on postoperative days 12 and 31 at which time patients were clinically examined for signs and symptoms of deep vein thrombosis, pulmonary embolism and adverse events. Bilateral compression ultrasonography was performed during these followup visits and venography was performed if ultrasonography was inconclusive. Patients were also instructed to report clinical signs earlier if they occurred, and physicians followed up by telephone every four days in patients who were randomized to dalteparin in between followup visits. Symptoms of deep vein thrombosis were confirmed with ultrasonography or venography and symptoms of pulmonary embolism were confirmed with ventilation-perfusion scans or angiography.

In this trial, the percent of patients with deep vein thrombosis was significantly decreased in those who received dalteparin prophylaxis versus control (1.5 percent versus 15.6 percent, $p=0.004$). All deep vein thromboses were distal and occurred in the operated leg while none were proximal or in the contralateral leg. Eight cases of deep vein thromboses were diagnosed at the first followup visit, 2 cases were diagnosed during the second followup visit, and 1 case was diagnosed on postoperative day 5 in the emergency room. Gender did not impact the effect of dalteparin versus placebo on the occurrence of deep vein thrombosis. One patient in the dalteparin group, who also had a distal deep vein thrombosis, developed a pulmonary embolism (1.5 percent) while none in the control group developed a pulmonary embolism (0 percent). No patients had major bleeding. There was no significant difference in the percent of patients who had minor bleeding in the dalteparin group versus control (12 percent versus 6 percent, $p=0.365$).

Strength of Evidence and Applicability of the Body of Evidence

In other orthopedic surgeries evaluated in this report, there were two trials which met inclusion criteria for Key Question 10; one trial in knee arthroscopy, one trial in Achilles tendon rupture repair, and no trials in elective spine surgery. Therefore the overall strength of evidence was insufficient for all outcomes evaluated in these patient populations. The applicability is

limited because only two trials were identified and therefore applicability is specific to the surgeries and interventions of these trials.

Key Question 11

In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (injectable low molecular weight heparin versus unfractionated heparin versus factor Xa inhibitors versus direct thrombin inhibitors) compared with mechanical interventions on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation?

No randomized controlled trials or controlled observational studies met our inclusion criteria for this Key Question and therefore all outcomes were rated as insufficient strength of evidence.

Discussion

A summary of the results with a strength of evidence rating of low, moderate, or high for Key Questions 1 through 8 of our CER can be found in Table 4. Evaluations for Key Questions 9 through 11 had insufficient strength of evidence and are not included. To see how our strength and applicability of evidence ratings were derived, please see Appendices H and I. For more detailed analysis of our results or to see results for comparisons with an insufficient strength of evidence rating, please see the results section for that Key Question. Although major orthopedic surgery is inclusive of total hip or knee replacement surgery and hip fracture surgery, the vast majority of literature evaluated hip or knee replacement surgery with very little evaluation of hip fracture surgery. No literature was found evaluating health related quality of life or post thrombotic syndrome as outcomes while harms such as bleeding leading to infection, bleeding leading to transfusion, readmission, and reoperation were rarely reported. No trials or studies were found to evaluate the comparative effectiveness of inferior vena cava filters with mechanical prophylaxis in major orthopedic surgery whereas comparative data of prophylaxis to no prophylaxis or between injectable and mechanical prophylaxis in other nonmajor orthopedic surgeries was very limited.

For several outcomes, although trials were designed to report events that occurred during the period of followup, many times there were no events which occurred. Therefore, the trial would be excluded from the pooled analysis in this report. Three Key Questions were more affected by the lack of outcomes occurring, including Key Question 4, 5, and 8. In Key Question 4, 25 percent of analyses with at least one randomized controlled trial had half or more excluded because no events occurred in the groups compared. The outcomes for which this occurred included fatal pulmonary embolism, pulmonary embolism, mortality due to bleeding, and major bleeding. In Key Question 5, the outcomes with the most comparisons which had half or more trials excluded because of no events included fatal pulmonary embolism, mortality due to bleeding, and major bleeding leading to reoperation. In Key Question 8, 21 percent of outcomes had half or more trials excluded because of no events, including fatal pulmonary embolism, mortality, mortality due to bleeding and bleeding leading to transfusion. Overall, in the majority of cases, although the trials were adequately designed to detect outcomes, the followup period was likely inadequate to capture the occurrence of events. Additionally, these outcomes were not commonly primary outcomes of the trials therefore underpowered to detect differences, which were not overcome by pooling since the events were rare.

Where applicable, we compare our results to those derived from previous meta-analyses as typified in Table 5 and Table 6. We used more recent search dates and generally used more restrictive inclusion and exclusion criteria than other meta-analyses including more stringent criteria for diagnosing deep venous thrombosis and pulmonary embolism endpoints. We also limited our evaluation to medications or mechanical devices available for use within the United States.

In Key Question 1 we limited our inclusion criteria to placebo or control arms of trials for pulmonary embolism and deep vein thrombosis outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. However, there are some limitations arising from having excluded other study designs. In contemporary surgical practice, the native incidence of deep vein thrombosis events is still relatively high but pulmonary embolism and bleeding events are rarer. In total hip replacement, total knee replacement, and hip fracture surgery, respectively, the incidence of deep vein thrombosis (39 percent, 53 percent, 47 percent), proximal deep vein

thrombosis (32 percent, 17 percent, --), distal deep vein thrombosis (30 percent, 30 percent, --), pulmonary embolism (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (6 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --) are reported in clinical trials.

There was high statistical heterogeneity between trials for most endpoints which likely reflects several study characteristics. The majority of trials did not specifically define the duration of followup and implied an immediate postoperative followup, although this could vary between studies. Additionally, the followup period may not reflect the period of highest risk for venous thromboembolic events after major orthopedic surgery. The countries and ethnicities where the trials were conducted in and when or how rigorously the endpoints were assessed for also varied. Our results are similar to that of previous pooled-analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001 where 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding as shown in Table 5.^{153,159,164,169,171} Using our stringent inclusion and exclusion criteria, including more stringent definitions of outcomes, and allowing trials and studies right up to the present day are strengths of our comparative effectiveness review.

In Key Question 2, several randomized controlled trials identified through our literature search evaluated different surgical characteristics on outcomes of interest including anesthetic regimen, cemented arthroplasty, tourniquet use, limb positioning, and fibrin adhesive use. However, few trials evaluated each characteristic and subsequently did not address all major orthopedic procedures. Additionally, most trials evaluated intermediate health outcomes and did not address final health outcomes and only one trial evaluated bleeding outcomes. As such, pooling was not possible. The surgical comparison with the most identified data was general anesthesia versus regional anesthesia. The impact of general versus regional anesthesia on several measures of deep vein thrombosis (overall, asymptomatic, proximal) was favorable to neutral for regional anesthesia while distal and symptomatic deep vein thrombosis, pulmonary embolism, and major bleeding were neutral. In a previous meta-analysis of 21 studies, regional anesthesia was associated with a nonsignificantly reduced odds of pulmonary embolism and a significantly reduced odds of deep vein thrombosis with no real impact on mortality versus general anesthesia.¹⁶² We did not pool the results from our six included trials because many of the trials did not maintain similar prophylaxis regimens between groups or between genders reducing our confidence in the similarity between the groups.

Although one trial compared spinal versus epidural anesthesia on the risk of deep vein thrombosis, no events occurred in the groups compared. The other surgical characteristics were too limited to make any determinations.

Patient characteristics were primarily evaluated in multivariate regression analyses of observational studies. Few characteristics were evaluated in multiple studies and often times when a significant finding was observed, the magnitude or direction of the effect was not reported. There were no data regarding harms. Patient characteristics that were found to significantly increase the odds of symptomatic objectively confirmed venous thromboembolism in all available studies included congestive heart failure (two studies), inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric fracture (one study), subtrochanteric fracture (one study), increased hemoglobin (one study), personal or familial history of venous thromboembolism, (one study), and varicose veins (one

study). Patient characteristics consistently found to increase the odds of pulmonary embolism (evaluated in one study each) included age and genitourinary infection while cardiovascular disease was found to decrease the odds of pulmonary embolism. The following characteristics showed a mixed effect on deep vein thrombosis: age (two studies showed a significant increase while one study showed no effect), obesity (one study showed a significant increase while one study showed no effect), and gender (one study showed a significant increase in females while one study showed gender had no effect). Metabolic syndrome increased the odds of symptomatic deep vein thrombosis while congestive heart failure increased the odds of proximal deep vein thrombosis in the single study that evaluated each covariate.

In Key Question 3, no trials or studies were available assessing whether DVT was correlated with, or a multivariate predictor of, PE. This data may be limited because the routine use of prophylaxis may have reduced the occurrence of deep vein thrombosis and the scheduled anticoagulant treatment for deep vein thrombosis once it was detected may have diminished the percentage that developed into pulmonary embolism. In one observational study in total knee replacement surgery, the overall occurrence of pulmonary embolism and the subset with symptomatic pulmonary embolism occurred more frequently in those with deep vein thrombosis. However the data were not adjusted for confounders and we cannot discern whether these variables are correlated or colinear. While we could have allowed inclusion of other literature types to describe the relationship between DVT and PE, we felt, as did our expert panel, that what our a priori defined inclusion criteria would provide the most compelling data should that literature exist. We feel that the other types of literature would not allow us to adequately answer this question.

In Key Question 4, the comparative balance of benefits to harms for providing pharmacologic prophylaxis versus no prophylaxis is favorable. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases proximal deep vein thrombosis and moderate evidence that prophylaxis decreases the risk of proximal or distal deep vein thrombosis in patients undergoing major orthopedic surgery. There is low evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major venous thromboembolism in patients undergoing major orthopedic surgery. Pharmacologic prophylaxis did not significantly impact pulmonary embolism in the base case analysis, although it was trending in that direction, and significantly reduced the risk of pulmonary embolism in the most stringent trials where they did not allow any background prophylaxis (such as compressions stockings) in the experimental groups. There is moderate evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis does not significantly impact nonfatal pulmonary embolism, mortality, symptomatic deep vein thrombosis or major bleeding in patients undergoing major orthopedic surgery. We cannot determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group. Our results are in general agreement with the six previous meta-analyses of trials comparing pharmacologic prophylaxis versus placebo/control in patients with major orthopedic surgery (Table 6).^{160,161,168,179,184,188} Four assessed low molecular weight heparin versus placebo/control, one evaluated low molecular weight heparin or unfractionated heparin versus placebo/control, and the last compared vitamin K antagonists versus placebo. In the most recent meta-analysis comparing low molecular weight heparins versus placebo, there was a significant reduction in the odds of nonfatal pulmonary embolism with nonsignificant reductions in

mortality and major bleeding. Deep vein thrombosis was not assessed in this meta-analysis but in the previous three meta-analyses was found to be significantly reduced with low molecular weight heparin use versus placebo/control. When either low molecular weight heparins or unfractionated heparin was compared with placebo/control deep vein thrombosis (overall, proximal, and deep) were significantly reduced but no significant impact on pulmonary embolism was found or death was found. In another meta-analysis, vitamin K antagonists significantly reduced pulmonary embolism and deep vein thrombosis but nonsignificantly increased major bleeding versus placebo.

The comparative balance of benefits to harms for providing mechanical prophylaxis versus no prophylaxis is possibly favorable but more data are needed to support this assumption. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal deep vein thrombosis in patients undergoing major orthopedic surgery, the power to detect these differences is low and the strength of evidence for all outcomes was insufficient. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use so benefits would likely overwhelm the risk of harms. In the only meta-analysis comparing mechanical prophylaxis (intermittent pneumatic compression and venous foot pump) versus control, the risk of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduced (Table 6).¹⁶⁰

In Key Question 5, we sought to determine the impact of therapy on numerous outcomes but were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, there was either a lack of evaluable data or no significant differences. We cannot determine if this means that there is a lack of effect versus a lack of power to show that it is significant.

Low molecular weight heparin agents, as a class, have a better comparative balance of benefits to harms versus unfractionated heparin with significantly fewer pulmonary embolisms, deep vein thromboses, proximal deep vein thromboses, major bleeding, and heparin induced thrombocytopenia events. The comparative balance of benefits to harms for low molecular weight heparins to other classes cannot be readily determined. Low molecular weight heparin agents are also superior to vitamin K antagonists at reducing measures of deep vein thromboses (any, asymptomatic, proximal, and distal) but increase major, minor, and surgical site bleeding. Since no significant differences were found in important final health outcomes, the relevance of these reductions in deep vein thrombosis needs to be considered. Low molecular weight heparin agents may be inferior to factor Xa inhibitors in terms of any, proximal, and distal deep vein thromboses but have a lower risk of major and minor bleeding. Observational data suggested low molecular weight heparin agents had decreased mortality although this was not supported by data pooled from randomized trials which showed no significant difference. The comparison of low molecular weight heparins agents to direct thrombin inhibitors is difficult because the occurrence of deep vein thrombosis is greater but the occurrence of distal deep vein thrombosis is less with low molecular weight heparin agents and while surgical site bleeding is higher with low molecular weight heparin therapy, the overall risk of serious bleeding was not significantly altered. Finally, when low molecular weight heparin agents are compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving low molecular weight heparin agents. The results of previous meta-analyses are in general agreement with the findings of our comparative effectiveness review. In six previous

meta-analyses, low molecular weight heparins were compared with unfractionated heparin in patients with major orthopedic surgery (Table 6)^{152,160,161,170,187,188} There were significant reductions in deep vein thrombosis (five of six meta-analyses), proximal deep vein thromboses (two of three meta-analyses with the third showing a nonsignificant reduction), and major bleeding (one of three meta-analyses with a nonsignificant reductions in the second and third) with low molecular weight heparins versus unfractionated heparin. There was a nonsignificant reduction in mortality (two of two meta-analyses), mixed effects on pulmonary embolism (one meta-analysis showing a significant reduction, one showing a nonsignificant increase the other showing a nonsignificant decrease), and a nonsignificant increase in any bleeding with low molecular weight heparins versus unfractionated heparin. In two previous meta-analyses, the impact of dabigatran versus enoxaparin in total hip and total knee arthroplasty outcomes was assessed.^{182,185} No significant differences in venous thromboembolism or major bleeding were seen. Four meta-analyses comparing vitamin K antagonists to low molecular weight heparins.^{161,168,170,181} The three meta-analyses evaluating deep vein thrombosis found a significant increase while the one of two meta-analyses evaluating major bleeding found a significant decrease and another found a nonsignificant decrease with vitamin K antagonist use versus low molecular weight heparins. One meta-analysis found a nonsignificant increase in pulmonary embolism and death while another found a nonsignificant increase in symptomatic pulmonary embolism. One meta-analysis compared the factor Xa inhibitor fondaparinux to the low molecular weight heparin enoxaparin and the odds of venous thromboembolism and proximal deep vein thrombosis was significantly reduced.

It is difficult to discern the comparative balance of benefits to harms for oral antiplatelet therapy versus mechanical prophylaxis or vitamin K antagonists. Oral antiplatelet therapy had significantly greater occurrence of any and distal deep vein thrombosis versus mechanical prophylaxis. In a controlled observational study, oral vitamin K antagonists had significantly fewer fatal pulmonary embolism events versus oral antiplatelet agents. In the only available randomized trial comparing vitamin K antagonists to oral antiplatelet agents, the same direction of effect was found suggesting vitamin K antagonist superiority but this was not significant. Mortality was higher in patients receiving aspirin versus warfarin in one observational study, was nonsignificantly trending in that direction in another observational study but showed no difference in a clinical trial. These results are characteristically similar to a previous meta-analysis which found that vitamin K antagonists nonsignificantly decreased overall deep vein thrombosis but nonsignificantly increased proximal deep vein thrombosis with no real difference in major hemorrhage (Table 6).¹⁶⁸

Unfractionated heparin, which was found to be inferior to low molecular weight heparin agents in the balance of benefits to harms, had a greater occurrence of death and major bleeding versus factor Xa inhibitors in an observational study (with no clinical trial data to support or refute the findings), had a greater occurrence of any and proximal deep vein thrombosis versus direct thrombin inhibitors, and had a greater occurrence of deep vein thrombosis versus mechanical prophylaxis. As such, it is likely inferior to factor Xa inhibitors in the balance of benefits to harms as well.

Patients receiving vitamin K antagonists had less occurrence of proximal deep vein thrombosis versus mechanical prophylaxis but with no other differences in other health outcomes or bleeding, it is hard to discern a difference in the balance of efficacy to harms between them. This is consistent with a previous meta-analysis that found nonsignificant decrease in proximal

deep vein thrombosis but nonsignificant increases in mortality, asymptomatic deep vein thrombosis, and major hemorrhage (Table 6).¹⁶⁸

In Key Question 6, there were no significant differences in pulmonary embolism (any, fatal, and nonfatal), mortality, and mortality due to bleeding between modalities within low molecular weight heparin and mechanical device classes but these evaluations were based on one or two trials with either no events or a very low number of events.

The balance of benefits to harms from using enoxaparin versus another low molecular weight heparin within the class (dalteparin or tinzaparin) is similar although the amount of literature available is very limited. No difference in the occurrence of deep vein thrombosis or proximal deep vein thrombosis occurred between low molecular weight heparins (enoxaparin versus either tinzaparin or dalteparin). No significant difference was seen in asymptomatic deep vein thrombosis between enoxaparin and dalteparin, symptomatic deep vein thrombosis between enoxaparin and tinzaparin, or distal deep vein thrombosis between enoxaparin and tinzaparin. For major bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. For surgical site bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. For heparin induced thrombocytopenia, one trial found no significant difference between enoxaparin and tinzaparin for this outcome.

The balance of benefits to harms for different mechanical modalities within a class cannot be determined with the current literature base. The Venaflow pneumatic compression device significantly reduced the occurrence of deep vein thrombosis or distal deep vein thrombosis versus the Kendall pneumatic compression device in the only trial but did not significantly reduce proximal deep vein thrombosis.

Intermittent compression stockings significantly reduced the occurrence of deep vein thrombosis or distal deep vein thrombosis versus graduated compression stockings but did not significantly reduce proximal deep vein thrombosis.

In the only observational study, two intermittent compression devices were compared (ActiveCare system versus Flowtron excel pump) and found to have a similar occurrence of deep vein thrombosis. Harms were not assessed in these trials or observational studies.

In Key Question 7, the balance of benefits to harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic surgery cannot be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis does not significantly impact nonfatal pulmonary embolism, mortality, or deep vein thrombosis subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There is moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of deep vein thrombosis versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes cannot be determined.

For Key Question 8, the balance of benefits to harms for prolonged versus shorter term prophylaxis in patients undergoing major orthopedic surgery is favorable. The impact of prolonging prophylaxis for 28 days or longer on events was compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. In base case analyses, prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed venous

thromboembolism, pulmonary embolism (overall and nonfatal), and deep vein thrombosis (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. While higher heterogeneity was found for symptomatic venous thromboembolism and deep vein thrombosis, the direction of effect was consistent between all of the trials. In base case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis. Four previous meta-analyses compared the impact of longer versus shorter duration pharmacologic prophylaxis and are in general agreement with our present comparative effectiveness review (Table 6).^{156,163,174,186} Decreases in deep venous thrombosis (overall, symptomatic, asymptomatic, and proximal) and venous thromboembolism were found with nonsignificant increases on minor bleeding but not major bleeding in these meta-analyses.

For Key Questions 9 and 11, there were no trials or studies that met our inclusion criteria. For Key Question 10, one trial was available for Achilles tendon rupture and for knee arthroscopy but no literature met inclusion criteria for elective spine surgery. Both of the available trials were small in size leading to limited power to detect differences between the groups compared. The comparative balance of benefits to harms for dalteparin therapy versus placebo or control is difficult to discern based on the scant data. In patients who had surgical repair of Achilles tendon rupture, the use of dalteparin versus placebo for six weeks did not significantly impact the incidence of total or proximal deep vein thrombosis. No patients developed a pulmonary embolism or major bleeding. In patients who had arthroscopic knee surgery, the use of dalteparin versus control led to significantly fewer patients with total or distal deep vein thrombosis. One patient in the dalteparin group developed a pulmonary embolism and also had a deep vein thrombosis. No patients had major bleeding and the occurrence of minor bleeding was not significantly different between the two groups.

In summary, in major orthopedic surgery, the incidence of DVT is appreciable but the risk of PE, major and minor bleeding is smaller. The balance of benefits to harms is favorable for providing prophylaxis to these patients and to extend the period of prophylaxis beyond the standard 7-10 days. The comparative balance of benefits to harms for LMWHs are superior to unfractionated heparin. Other interclass comparisons either could not be made due to lack of data, showed similarities between classes on outcomes, or had offsetting effects where benefits of one class on efficacy was tempered by an increased risk of bleeding. The balance of benefits to harms for dual pharmacologic plus mechanical prophylaxis versus either strategy alone could not be determined. We could not determine the impact of IVC filters on outcomes or the impact of prophylaxis on the nonmajor orthopedic surgeries evaluated. We present the limitations of current research as well as future research needs which may help to shape future practice and policy in this clinical area.

Future Research

Limitations of Current Research

- In total hip replacement, total knee replacement, and hip fracture surgery there are numerous limitations to the current literature base that need to be appreciated.
 - While we found that there is a real risk of developing deep vein thrombosis, pulmonary embolism, and major bleeding after undergoing major orthopedic surgery, there are inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism. We were not even able to determine that deep vein thrombosis is an independent predictor of pulmonary embolism. With prophylaxis to prevent deep vein thrombosis and pulmonary embolism and the use of active treatment of deep vein thrombosis to prevent pulmonary embolism, it is difficult to assess this linkage. In addition, we had no data to assess the linkage between deep vein thrombosis and other final health outcomes. This creates a dilemma for patients, healthcare decision makers, and clinicians when the endpoint most commonly evaluated in the prophylaxis trials is deep vein thrombosis.
 - In many studies a more specific duration of followup beyond “postoperative” was unclear and may be implied as a more immediate postoperative followup rather than a longer term followup. It is unclear whether the period of highest risk for outcomes is inclusive in “postoperative” followup. Few trials reported a longer term followup such as postdischarge.
 - Other than showing the superiority in the balance of benefits to harms for low molecular weight heparins versus unfractionated heparin, whether one class is superior to another class cannot be clearly determined. In a few cases, there are offsetting benefit and harms effects and in many cases, there just is not ample evidence to assess. While it seems that low molecular weight heparins (enoxaparin, dalteparin, tinzaparin) have similar effects, we cannot determine if an agent within any other class is superior to another agent within the same class.
 - The large variety and number of mechanical devices makes it hard to know how data can be extrapolated from one device to others in the same or different classes. Mechanical device trials are by and large devoid of harms evaluations.
 - We cannot discern the comparative benefits and harms of using both pharmacologic and mechanical prophylaxis versus either modality alone.
 - Further research is needed to determine independent predictors of intermediate, final health, and harms outcomes. Current literature is too scant to reliably determine the impact of surgical or patient characteristics on these outcomes.
 - We could not determine the comparative benefits and harms of using inferior vena cava filters with mechanical prophylaxis in major orthopedic surgery as no literature met our inclusion criteria.
- When we assess orthopedic surgeries other than total hip replacement, total knee replacement or hip fracture surgery, we do not have an adequate literature base to determine benefits or harms.

Future Research Avenues

- In total hip replacement, total knee replacement, and hip fracture surgery there are several avenues for future research:
 - Since the linkage between deep vein thrombosis and venous thromboembolism, pulmonary embolism, postthrombotic syndrome, or mortality has not been shown, future comparative trials should focus on these final health outcomes or should explicitly show the linkage between deep vein thrombosis and these final health outcomes. It would not be sufficient just to show a correlation between these outcomes.
 - Future trials evaluating prophylaxis within major orthopedic surgery should more clearly define the period of followup and include a followup period beyond the hospital stay to include the period of highest risk for final health outcomes.
 - Future trials evaluating prophylaxis within major orthopedic surgery should include more outcomes assessing harms such as bleeding leading to infection, bleeding leading to transfusion, readmission and reoperation to provide more information for the comparative balance of benefits to harms. Additionally patient important outcomes such as health related quality of life and post thrombotic syndrome should be included.
 - Future observational studies should be designed to determine if there are surgical or patient factors that predict the occurrence of these outcomes. We have identified several promising predictors but need future evaluations to help determine their importance.
 - For regional versus general surgery, an adequately powered randomized controlled trial is needed to determine if anesthesia type impacts patient outcomes.
 - Future within class and between class comparative trials are needed. In several classes, both oral and intravenous methods of pharmacologic prophylaxis will be available and should be directly evaluated. More attention to assessing for final health outcomes and harms will be needed in these trials. Especially given the benefits of prolonged prophylaxis versus short term prophylaxis, the impact of oral therapy on patient perceived quality of life will be an important endpoint to consider. If a greater number of between class trials are conducted, mixed treatment comparison meta-analyses could be conducted to assess for indirect comparisons but presently, the literature base seems too sparse to conduct such an analysis.
 - Future trials comparing the benefits and harms of using both dual modality versus single modality prophylaxis alone are needed.
 - Further research is needed to determine independent predictors of intermediate, final health, and harms outcomes. Current literature is too scant to reliably determine the impact of surgical or patient characteristics on these outcomes
 - Future trials comparing the benefits and harms of using inferior vena cava filters versus mechanical prophylaxis are needed.
- Future trials in nonmajor orthopedic surgeries should determine whether or not prophylaxis is superior to control and the comparative effectiveness of different prophylactic options.

Addendum

After this report was updated, the Food and Drug Administration approved an oral direct factor Xa inhibitor, rivaroxaban, for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing knee or hip replacement surgery.¹⁹⁹ Four phase III trials have been completed at this time.²⁰⁰⁻²⁰³ Since this drug did not carry an FDA approved indication until recently, rivaroxaban did not meet the inclusion criteria and was not included in this report. We find these trials relevant since they provide new information for an additional between class comparison (oral direct factor Xa inhibitor versus injectable low-molecular weight heparin) in Key Question 5. The main findings of the four trials and the outcomes reported in these trials that are consistent with the methodology of this report are described here.

The four Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) trials compared various regimens of rivaroxaban and enoxaparin, in total hip or knee replacement surgery (Table 16). All four trials were determined to be of good methodological quality and all evaluated either a per-protocol, modified intention to treat, or safety population for a given outcome.

Table 16. The RECORD trials

Trial, Population	Intervention	Comparator
RECORD 1 THR	Rivaroxaban 10mg po QD, started 6-8h postoperatively, for 35±4d	Enoxaparin 40mg SQ daily, started evening before surgery, for 36±4d
RECORD 2 THR	Rivaroxaban 10mg po QD, started 6-8h postoperatively, for 35±4d	Enoxaparin 40mg SQ daily, started evening before surgery, for 13±2d
RECORD 3 TKR	Rivaroxaban 10mg po QD, started 6-8h postoperatively, for 12±2d	Enoxaparin 40mg SQ daily, started evening before surgery, for 13±2d
RECORD 4 TKR	Rivaroxaban 10mg po QD, started 6-8h postoperatively, for 12±2d	Enoxaparin 30mg Q12h, started 12-24h after wound closure, for 12±2d

d = days; h = hours; mg = milligrams; RECORD = Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism; SQ = subcutaneously; THR = total hip replacement; TKR = total knee replacement; po = by mouth; Q = daily

RECORD 1²⁰⁰: This trial was designed to evaluate extended duration prophylaxis in total hip replacement surgery and randomized 4,541 patients to receive either rivaroxaban or enoxaparin (Table 16). The mean duration of followup was 33.4 days and 33.7 days in the rivaroxaban and enoxaparin groups, respectively. Symptomatic venous thromboembolism was not significantly different in the rivaroxaban group compared with enoxaparin during the treatment [risk difference (RD) -0.1 (-0.6 to 0.1)] or followup [RD -0.1 (-0.4 to 0.1)] period. Major venous thromboembolism was a composite of proximal deep vein thrombosis, nonfatal pulmonary embolism or death from venous thromboembolism. The risk of major venous thromboembolism was significantly decreased in the rivaroxaban group compared with enoxaparin [RD -1.7 percent (-2.5 to -1.0)]. Death during treatment [RD 0.0 (-0.4 to 0.4)] or death during followup [RD 0.1 (-0.2 to 0.4)] was not significantly different in the rivaroxaban group compared with enoxaparin. Nonfatal pulmonary embolism was not significantly different in the rivaroxaban group compared with enoxaparin [RD 0.2 (-0.1 to 0.6)].

The risk of total deep vein thrombosis [RD -2.7 (-3.7 to -1.7)] or proximal deep vein thrombosis [RD -1.9 (-2.7 to -1.2)] was decreased with rivaroxaban compared with enoxaparin although the risk of distal deep vein thrombosis was not significantly impacted [RD -0.7 (-1.5 to 0.0)]. There was no difference in the risk of major bleeding in the rivaroxaban group compared with enoxaparin [RD 0.2 (-0.1 to 0.5)]. The incidence of nonmajor bleeding was similar in both

groups; rivaroxaban 128/2209 (5.8 percent), enoxaparin 129/2224 (5.8 percent), ($p=0.955$). There was one death from bleeding (0.05 percent) in the rivaroxaban group and none in the enoxaparin group ($p=0.995$). Two cases (0.09 percent) of bleeding leading to reoperation occurred in the rivaroxaban group while 1 case (0.04 percent) occurred in the enoxaparin group ($p=0.995$).

RECORD 2²⁰¹: This trial was designed to evaluate extended duration prophylaxis with rivaroxaban to short-term prophylaxis with enoxaparin in total hip replacement surgery (Table 16). A total of 2,509 patients were randomized to receive either rivaroxaban or enoxaparin and the mean duration of followup was 33.5 days and 12.4 days in the rivaroxaban and enoxaparin groups, respectively. Symptomatic venous thromboembolism was significantly decreased in the rivaroxaban group compared with enoxaparin during treatment [absolute risk reduction (ARR) 1.0 (0.3 to 1.8)] but not during the followup period [ARR 0.1 (-0.2 to 0.4)]. Major venous thromboembolism was a composite of proximal deep vein thrombosis, nonfatal pulmonary embolism or death from venous thromboembolism. The risk of major venous thromboembolism was significantly decreased in the rivaroxaban group compared with enoxaparin [ARR 4.5 (3.0 to 6.0)]. Death during treatment [ARR 0.5 (-0.2 to 1.1)] or death during followup [ARR 0.2 (-0.1 to 0.6)] was not significantly different in the rivaroxaban group compared with enoxaparin. Nonfatal pulmonary embolism was not significantly different in the rivaroxaban group compared with enoxaparin [ARR 0.3 (-0.2 to 1.1)].

The risk of total deep vein thrombosis [ARR 6.5 (4.5 to 8.5)], proximal deep vein thrombosis [ARR 4.5 (2.9 to 6.0)] and distal deep vein thrombosis [ARR 2.0 (0.7 to 3.3)] was decreased with rivaroxaban compared with enoxaparin. One major bleeding episode occurred in each group (0.08 percent in each group, $p=0.480$) and there were no fatal bleeding events or bleeding leading to reoperation events. The incidence of nonmajor bleeding was 80/1228 (6.5 percent) in the rivaroxaban group and 67/1229 (5.5 percent) in the enoxaparin group ($p=0.305$).

RECORD 3²⁰²: This trial was designed to evaluate the use of rivaroxaban compared with once daily enoxaparin for venous thromboembolism prophylaxis in total knee replacement surgery (Table 16). A total of 2,556 patients were randomized to receive either rivaroxaban or enoxaparin and the mean duration of followup was 11.9 days and 12.5 days in the rivaroxaban and enoxaparin groups, respectively. Symptomatic venous thromboembolism was significantly decreased in the rivaroxaban group compared with enoxaparin during treatment [RD -1.3 (-2.2 to -0.4)] but not during the followup period [RD 0.2 (-0.3 to 0.6)]. Major venous thromboembolism was a composite of proximal deep vein thrombosis, nonfatal pulmonary embolism or death from venous thromboembolism. The risk of major venous thromboembolism was significantly decreased in the rivaroxaban group compared with enoxaparin [RD -1.6 (-2.8 to -0.4)]. Death during treatment [RD -0.2 (-0.6 to 0.2)] or death during followup [RD -0.3 (-0.8 to 0.0)] was not significantly different in the rivaroxaban group compared with enoxaparin. Nonfatal pulmonary embolism was not significantly different in the rivaroxaban group compared with enoxaparin [RD -0.3 (-0.8 to 0.0)].

The risk of total deep vein thrombosis [RD -8.4 (-11.7 to -5.2)] and distal deep vein thrombosis [RD -7.3 (-10.4 to -4.3)] was decreased with rivaroxaban compared with enoxaparin but the risk of proximal deep vein thrombosis was not significantly impacted [RD -1.1 (-2.3 to 0.1)]. No significant difference in the rate of major bleeding during treatment was found, with 7/1220 (0.6 percent) cases in the rivaroxaban group and 6/1239 (0.5 percent) in the enoxaparin group ($p=0.77$). No fatal bleeding episodes occurred. Five cases (0.4 percent) of bleeding leading to reoperation occurred in the rivaroxaban group and 4 cases (0.3 percent) occurred in the

enoxaparin group ($p=0.981$). The incidence of nonmajor bleeding was 53/1220 (4.3 percent) in the rivaroxaban group and 54/1239 (4.4 percent) in the enoxaparin group ($p=0.935$).

RECORD 4²⁰³: This trial was designed to evaluate the use of rivaroxaban compared with twice daily enoxaparin for venous thromboembolism prophylaxis in total knee replacement surgery (Table 16). A total of 3,148 patients were randomized to receive either rivaroxaban or enoxaparin and the mean duration of followup was 11.7 days and 11.0 days in the rivaroxaban and enoxaparin groups, respectively. Symptomatic venous thromboembolism was not significantly different in the rivaroxaban group compared with enoxaparin during treatment [RD -0.47 (-1.16 to 0.23)] or during the followup period [RD 0.00 (-0.32 to 0.32)]. Major venous thromboembolism was a composite of proximal deep vein thrombosis, nonfatal pulmonary embolism or death from venous thromboembolism. The risk of major venous thromboembolism was not significantly different in the rivaroxaban group compared with enoxaparin in both the per-protocol [RD -0.37 (-1.34 to 0.60)] and modified intention to treat populations [RD -0.80 (-1.82 to 0.22)]. Death during treatment [RD -0.07 (-0.46 to 0.30)] or death during followup [RD 0.06 (-0.35 to 0.50)] was not significantly different in the rivaroxaban group compared with enoxaparin. Pulmonary embolism [RD -0.20 (-0.75 to 0.30)] and nonfatal pulmonary embolism [RD -0.27 (-0.8 to 0.21)] was not significantly different in the rivaroxaban group compared with enoxaparin.

Asymptomatic deep vein thrombosis occurred in 55/965 (5.7 percent) of rivaroxaban patients and 76/959 (7.9 percent) of enoxaparin patients ($p=0.065$). Of those cases, 3 and 13 were proximal ($p=0.08$) and 52 and 63 were distal ($p=0.08$), in the rivaroxaban and enoxaparin groups respectively. Symptomatic deep vein thrombosis occurred in 6/965 (0.6 percent) of rivaroxaban patients and 10/959 (1.0 percent) of enoxaparin patients ($p=0.444$). No significant difference in the rate of major bleeding during treatment was found, with 10/1526 (0.7 percent) cases in the rivaroxaban group and 4/1508 (0.3 percent) in the enoxaparin group ($p=0.1096$). One fatal bleeding episode (0.07 percent) occurred in the rivaroxaban group and none in the enoxaparin group ($p=0.995$). Five cases (0.3 percent) of bleeding leading to reoperation occurred in the rivaroxaban group and 2 (0.1 percent) occurred in the enoxaparin group ($p=0.459$). The incidence of nonmajor bleeding was 155/1526 (10.2 percent) in the rivaroxaban group and 138/1508 (9.2 percent) in the enoxaparin group ($p=0.381$).

Acronyms/Abbreviations

AOR	Adjusted odds ratio
CI	Confidence interval
EPC	Evidence-based Practice Center
Mg	Milligrams
NNH	Number needed to harm
NNT	Number needed to treat
OR	Peto's odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative risk

References

1. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:381S-453S. PMID: 18574271
2. American Academy of Orthopaedic Surgeons. Clinical guideline on prevention of pulmonary embolism in patients undergoing total hip or knee arthroplasty. www.guideline.gov/content.aspx?id=10850.
3. Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians Guidelines for Venous Thromboembolism Prevention in Hip and Knee Arthroplasty Differ: What are the implications for clinicians and patients? *Chest* 2009;135:513-20. PMID: 19201714
4. Haas SB, Barrack RL, Westrich G, Lachiewicz PF. Venous thromboembolic disease after total hip and knee arthroplasty. *J Bone Joint Surg Am* 2008;90:2764-80. PMID: 19047723
5. Sharrock NE, Go G, Harpel PC, Ranawat CS, Sculco TP, Salvati EA. The John Charnley Award: Thrombogenesis during total hip arthroplasty. *Clin Orthop Relat Res* 1995;319:16-27. PMID: 7554626
6. Salvati EA, Pellegrini VD, Sharrock NE, Lotke PA, Murray DM, Potter H. Recent advances in venous thromboembolic prophylaxis during and after total hip replacement. *J Bone Joint Surg Am* 2000;82:252-70. PMID: 10682733
7. Poss R, Thornhill TS, Ewalt FC, et al. Factors influencing the incidence and outcomes of infection following total joint arthroplasty. *Clin Orthop Relat Res* 1984;182:117-26. PMID: 6692605
8. Saleh K, Olson M, Resig S, et al. Predictors of wound infection in hip and knee joint replacement: results from a 20 year surveillance program. *J Orthop Res* 2002;20:506-15. PMID: 12038624
9. Egermayer P TG. The clinical significance of pulmonary embolism: uncertainties and implications for treatment-a debate. *J Intern Med* 1997;241:5-10. PMID: 9042087
10. Goodman LR. Small pulmonary emboli: what do we know? *Radiology* 2005;234:654-8. PMID: 15734923
11. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA* 1990;263:2753-9. PMID: 2332918
12. Biello DR, Mattar AG, McKnight RC, et al. Ventilation-perfusion studies in suspected pulmonary embolism. *AJR* 1979;133:1033-7. PMID: 116491
13. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77. PMID: 16596572
14. Higgins JPT, Green S. (editors): *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org. Posted February 2008. Updated February 2008.
15. Fu R, Gartlehner G, Grant M, et al. Conducting Quantitative Synthesis When Comparing Medical Interventions: AHRQ and the Effective Health Care Program. In: Agency for Healthcare Research and Quality. *Methods Guide for Comparative Effectiveness Reviews* [posted October 2010]. Rockville, MD. Available at: <http://effectivehealthcare.ahrq.gov/>.
16. Owens D, Lohr K, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions: AHRQ and the effective health care program. *J Clin Epidemiol* 2010;63:513-23. PMID: 19595577

17. Atkins D, Chang S, Gartlener G, et al. Assessing the applicability of studies when comparing medical interventions. Agency for Healthcare Research and quality; January 2011. Methods guide for comparative effectiveness reviews. AHRQ Publication No. 11-EHC019-EF. Available at <http://effectivehealthcare.ahrq.gov>.
18. Barden B, Kröger K, Löer F. Intraoperative Dopplersonography of the femoral vein for maintenance of venous flow in a hip endoprosthesis. *Unfallchirurg* 2001;104:138-42.
19. Farag E, Dilger J, Brooks P, et al. Epidural analgesia improves early rehabilitation after total knee replacement. *J Clin Anesth* 2005;17:281-5. PMID: 15950853
20. Jorgensen LN, Rasmussen LS, Nielsen PT, et al. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. *Br J Anaesth* 1991;66:8-12. PMID: 1997063
21. Kim YH, Oh SH, Kim JS. Incidence and natural history of deep-vein thrombosis after total hip arthroplasty. A prospective and randomised clinical study. *J Bone Joint Surg Br* 2003;85:661-5. PMID: 12892186
22. Laupacis A, Rorabeck C, Bourne R, et al. The frequency of venous thrombosis in cemented and non-cemented hip arthroplasty. *J Bone Joint Surg Br* 1996;78:210-2. PMID: 8666626
23. Levy O, Martinowitz U, Oran A, et al. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. *J Bone Joint Surg Am* 1999;81:1580-8. PMID: 10565650
24. Mitchell D, Friedman RJ, Baker JD, 3rd, et al. Prevention of thromboembolic disease following total knee arthroplasty. Epidural versus general anesthesia. *Clin Orthop* 1991;(269):109-12. PMID: 1864027
25. Nielsen PT, Jorgensen LN, Albrecht-Beste E, et al. Lower thrombosis risk with epidural blockade in knee arthroplasty. *Acta Orthop Scand* 1990;61:29-31. PMID: 2186591
26. Pitto RP, Hamer H, Fabiani R, et al. Prophylaxis against fat and bone-marrow embolism during total hip arthroplasty reduces the incidence of postoperative deep-vein thrombosis: a controlled, randomized clinical trial. *J Bone Joint Surg Am* 2002;84-A:39-48. PMID: 11792778
27. Planes A, Samama MM, Lensing AW, et al. Prevention of deep vein thrombosis after hip replacement--comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost* 1999;81:22-5. PMID: 10348714
28. Thorey F, Stukenborg-Colsman C, Windhagen H, et al. The effect of tourniquet release timing on perioperative blood loss in simultaneous bilateral cemented total knee arthroplasty: A prospective randomized study. *Technology and Health Care* 2008;16:85-92. PMID: 18487854
29. Westrich GH, Winiarsky R, Betsy M, et al. Effect on deep venous thrombosis with flexion during total knee arthroplasty. *HSS Journal* 2006;2:148-53. PMID: 18751828
30. Williams-Russo P, Sharrock NE, Haas SB, et al. Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. *Clin Orthop* 1996;199-208. PMID: 8895639
31. Abdel-Salam A, Eyres K. Effects of tourniquet during total knee arthroplasty: A prospective randomised study. *J Bone Joint Surg* 1995;77-B:250-3. PMID: 7706340
32. McKenzie PJ, Wishart HY, Gray I, et al. Effects of anaesthetic technique on deep vein thrombosis. A comparison of subarachnoid and general anaesthesia. *Br J Anaesth* 1985;57:853-7. PMID: 4027101
33. Wakankar HM, Nicholl JE, Koka R, et al. The tourniquet in total knee arthroplasty. *J Bone Joint Surg* 1999;81-B:30-3. PMID: 10067997
34. Modig J, Hjelmstedt A, Sahlstedt B, et al. Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. *Acta Chir Scand* 1981;147:125-30. PMID: 7324741

35. Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986;56:53-6. PMID: 3535158
36. Chin PL, Amin MS, Yang KY, et al. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial. *J Orthop Surg* 2009;17:1-5. PMID: 19398783
37. Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *J Bone Joint Surg Br* 1992;74:45-9. PMID: 1732264
38. Fuji T, Ochi T, Niwa S, et al. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. *J Orthop Sci* 2008;13:442-51. PMID: 18843459
39. Jorgensen PS, Knudsen JB, Broeng L, et al. [The thromboprophylactic effect of low molecular weight heparin (Fragmin) in hip fracture surgery. A placebo controlled trial]. *Ugeskr Laeger* 1993;155:706-8. PMID: 8384388
40. Jorgensen PS, Knudsen JB, Broeng L, et al. The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. *Clin Orthop* 1992;(278):95-100. PMID: 1314147
41. Kim YH, Choi IY, Park MR, et al. Prophylaxis for deep vein thrombosis with aspirin or low molecular weight dextran in Korean patients undergoing total hip replacement. A randomized controlled trial. *Int Orthop* 1998;22:6-10. PMID: 9549575
42. Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991;62:33-8. PMID: 1848385
43. McKenna R, Galante J, Bachmann F, et al. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *Br Med J* 1980;280:514-7. PMID: 6989432
44. Samama CM, Clergue F, Barre J, et al. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. *Br J Anaesth* 1997;78:660-5. PMID: 9215015
45. Sorensen JV, Borris LC, Lassen MR, et al. Levels of thrombin--antithrombin-III complex and factor VIII activity in relation to post-operative deep vein thrombosis and influence of prophylaxis with a low-molecular-weight heparin. *Blood Coagul Fibrinolysis* 1990;1:389-92. PMID: 1966794
46. Sorensen JV, Borris LC, Lassen MR, et al. Association between plasma levels of tissue plasminogen activator and postoperative deep vein thrombosis--influence of prophylaxis with a low molecular weight heparin. The Venous Thrombosis Group. *Thromb Res* 1990;59:131-8. PMID: 2169077
47. Torholm C, Broeng L, Jorgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *J Bone Joint Surg Br* 1991;73:434-8. PMID: 1670445
48. Turpie AG. Enoxaparin prophylaxis in elective hip surgery. *Acta Chir Scand Suppl* 1990;556:103-7. PMID: 1963014
49. Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986;315:925-9. PMID: 3531851
50. WelinBerger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. *Acta Orthop Scand* 1982;53:937-45. PMID: 6184938
51. Wilson NV, Das SK, Kakkar VV, et al. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. *J Bone Joint Surg Br* 1992;74:50-2. PMID: 1732265
52. Warwick D, Bannister G, Glew D, et al. Perioperative low-Molecular-Weight Heparin: Is it effective and safe? *J Bone Joint Surg* 1995;77-B:715-9. PMID: 7559695

53. Fuji T, Fuijita S, Ujihira T, et al. Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo. *J Arthroplasty* 2010;25:1267-74. PMID: 19854610
54. A multicenter, multinational, randomized double-blind comparison study of subcutaneous Org31540/SR90107A versus enoxaparin 40 mg o.d. in the prevention of deep vein thrombosis and symptomatic pulmonary embolism in hip fracture surgery. (PENTHIFRA). Study No: EFC2698. GlaxoSmithKline Clinical Trial Register 2005;
55. Avikainen V, von Bonsdorff H, Partio E, et al. Low molecular weight heparin (enoxaparin) compared with unfractionated heparin in prophylaxis of deep venous thrombosis and pulmonary embolism in patients undergoing hip replacement. *Ann Chir Gynaecol* 1995;84:85-90. PMID: 7645915
56. Bailey JP, Kruger MP, Solano FX, et al. Prospective randomized trial of sequential compression devices vs low-dose warfarin for deep venous thrombosis prophylaxis in total hip arthroplasty. *J Arthroplasty* 1991;6:S29-35. PMID: 1774568
57. Barre J, Pfister G, Potron G, et al. [Comparison of the efficacy and tolerance of Kabi 2165 and standard heparin in the prevention of deep venous thrombosis in total hip prosthesis]. *J Mal Vasc* 1987;12:90-5. PMID: 2834500
58. Bonneux IM, Bellemans J, Fabry G. Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin. *Knee* 2006;13:118-21. PMID: 16387501
59. Cofrancesco E, Cortellaro M, Corradi A, et al. Coagulation activation markers in the prediction of venous thrombosis after elective hip surgery. *Thromb Haemost* 1997;77:267-9. PMID: 9157579
60. Colwell CW, Jr, Collis DK, Paulson R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. *J Bone Joint Surg Am* 1999;81:932-40. PMID: 10428124
61. Colwell CW, Jr, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. *J Bone Joint Surg Am* 1994;76:3-14. PMID: 8288662
62. Colwell CW, Jr, Spiro TE, Trowbridge AA, et al. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. Enoxaparin Clinical Trial Group. *Clin Orthop* 1995;(321):19-27. PMID: 7497668
63. Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989;19:5-12. PMID: 2537787
64. Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001;345:1298-304. PMID: 11794148
65. Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005;3:103-11. PMID: 15634273
66. Eriksson BI, Dahl OE, Rosencranch N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-85. PMID: 17764540

67. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56. PMID: 17869635
68. Eriksson BI, Ekman S, Kalebo P, et al. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. *Lancet* 1996;347:635-9. PMID: 8596376
69. Eriksson BI, Ekman S, Lindbratt S, et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* 1997;79:326-33. PMID: 9070519
70. Eriksson BI, Eriksson E, Risberg B. Impaired fibrinolysis and postoperative thromboembolism in orthopedic patients. *Thromb Res* 1991;62:55-64. PMID: 1853306
71. Eriksson BI, Kalebo P, Anthymyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. *J Bone Joint Surg Am* 1991;73:484-93. PMID: 2013587
72. Eriksson BI, Kalebo P, Risberg B. Clinical experience of a low molecular weight heparin (Fragmin) in the prevention of thromboembolism after total hip replacement. *Semin Thromb Hemost* 1993;19:122-7. PMID: 8395714
73. Eriksson BI, Wille-Jorgensen P, Kalebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997;337:1329-35. PMID: 9358126
74. Fauno P, Suomalainen O, Rehnberg V, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. *J Bone Joint Surg Am* 1994;76:1814-8. PMID: 7989386
75. Fitzgerald RH,Jr, Spiro TE, Trowbridge AA, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am* 2001;83-A:900-6. PMID: 11407799
76. Francis CW, Pellegrini VD,Jr, Marder VJ, et al. Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992;267:2911-5. PMID: 1583760
77. Francis CW, Pellegrini VD,Jr, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. *J Bone Joint Surg Am* 1997;79:1365-72. PMID: 9314399
78. Greinacher A, Eichler P, Albrecht D, et al. Antihirudin antibodies following low-dose subcutaneous treatment with desirudin for thrombosis prophylaxis after hip-replacement surgery: incidence and clinical relevance. *Blood* 2003;101:2617-9. PMID: 12393696
79. Haas SB, Insall JN, Scuderi GR, et al. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am* 1990;72:27-31. PMID: 2404020
80. Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993;329:1370-6. PMID: 8413432
81. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparisons. *Arch Intern Med* 2000;160:2199-207. PMID: 10904464
82. Kennedy JG, Soffe KE, Rogers BW, et al. Deep vein thrombosis prophylaxis in hip fractures: A comparison of the arteriovenous impulse system and aspirin. *Journal of Trauma - Injury, Infection and Critical Care* 2000;48:268-72. PMID: 10697085

83. Lassen M, Bauer K, Eriksson B, et al. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002;359:1715-20. PMID: 12049858
84. Lassen MR, Davidson BL, Gallus A, et al. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007;5:2368-75. PMID: 17868430
85. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med* 1996;124:619-26. PMID: 8607589
86. Levine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991;114:545-51. PMID: 1848054
87. Levine MN, Planes A, Hirsh J, et al. The relationship between anti-factor Xa level and clinical outcome in patients receiving enoxaparine low molecular weight heparin to prevent deep vein thrombosis after hip replacement. *Thromb Haemost* 1989;62:940-4. PMID: 2556813
88. Lotke PA, Palevsky H, Keenan AM, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop* 1996;:251-8. PMID: 8595765
89. Menzin J, Richner R, Huse D, et al. Prevention of deep-vein thrombosis following total hip replacement surgery with enoxaparin versus unfractionated heparin: a pharmacoeconomic evaluation. *Ann Pharmacother* 1994;28:271-5. PMID: 8173149
90. Paiement G, Wessinger SJ, Waltman AC, et al. Low-dose warfarin versus external pneumatic compression for prophylaxis against venous thromboembolism following total hip replacement. *J Arthroplasty* 1987;2:23-6. PMID: 3572408
91. Planes A, Vochelle N, Mazas F, et al. [Double-blind randomized comparative study of enoxaparin and standard heparin in the prevention of thromboembolic disease during insertion of total hip replacement]. *Rev Med Interne* 1988;9:327-33. PMID: 2841742
92. Planes A, Vochelle N, Mazas F, et al. [The use of enoxaparine in preventing deep venous thrombosis following total hip prosthesis. Randomized multicenter prospective trial]. *Rev Chir Orthop Reparatrice Appar Mot* 1988;74:215-8. PMID: 2852830
93. Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988;60:407-10. PMID: 2853459
94. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9. PMID: 18534438
95. Santori FS, Vitullo A, Stopponi M, et al. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Joint Surg Br* 1994;76:579-83. PMID: 8027144
96. Schwartzmann CR, Cavalieri CR, Drumond SN, et al. Randomized, comparative, open study to assess the efficacy and safety of enoxaparin compared with unfractionated heparin in the prophylaxis of venous thromboembolism in patients undergoing total hip arthroplasty. *Revista Brasileira De Ortopedia* 1996;31:797-808. PMID: Embase 1996366023
97. Senaran H, Acaroglu E, Ozdemir HM, et al. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. *Arch Orthop Trauma Surg* 2006;126:1-5. PMID: 16333632
98. Stone MH, Limb D, Campbell P, et al. A comparison of intermittent calf compression and enoxaparin for thromboprophylaxis in total hip replacement. A pilot study. *Int Orthop* 1996;20:367-9. PMID: 9049766

99. Turpie AG, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002;359:1721-6. PMID: 12049860
100. Warkentin TE, Roberts RS, Hirsh J, et al. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch Intern Med* 2003;163:2518-24. PMID: 14609790
101. Warwick D, Harrison J, Glew D, et al. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *J Bone Joint Surg Am* 1998;80:1158-66. PMID: 9730125
102. Warwick D, Harrison J, Whitehouse S, et al. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. *J Bone Joint Surg Br* 2002;84:344-50. PMID: 12002490
103. Warkentin T, Levine M, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5. PMID: 7715641
104. Rader CP, Kramer C, König A, et al. Low-molecular-weight heparin and partial thromboplastin time-adjusted unfractionated heparin in thromboprophylaxis after total knee and total hip arthroplasty. *J arthroplasty* 1998;13:180-5. PMID: 9526211
105. Monreal M, Lafoz E, Navarro A, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma* 1989;29:873-5. PMID: 2544742
106. Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001;345:1305-10. PMID: 11794149
107. Dabigatran Etxilate vs Enoxaparin in Prevention of Venous Thromboembolism (VTE) Post Total Knee Replacement. Available at: <http://clinicaltrials.gov/ct2/show/NCT00152971>. Accessed Oct. 22, 2010.
108. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. *Haemostasis* 1999;29:310-7. PMID: 10844404
109. Bara L, Planes A, Samama MM. Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery. *Br J Haematol* 1999;104:230-40. PMID: 10050702
110. Lachiewicz PF, Kelley SS, Haden LR. Two mechanical devices for prophylaxis of thromboembolism after total knee arthroplasty. A prospective, randomised study. *Journal of Bone and Joint Surgery - Series B* 2004;86:1137-41. PMID: 15568526
111. Planes A. An equivalence study of two low-molecular-weight heparins in the prevention and treatment of deep-vein thrombosis after total hip replacement. *Semin Thromb Hemost* 2000;26:57-60. PMID: 11011808
112. Ryan MG, Westrich GH, Potter HG, et al. Effect of mechanical compression on the prevalence of proximal deep venous thrombosis as assessed by magnetic resonance venography. *J Bone Joint Surg Am* 2002;84-A:1998-2004. PMID: 12429761
113. Silbersack Y, Taute BM, Hein W, et al. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. *J Bone Joint Surg Br* 2004;86:809-12. PMID: 15330019
114. Edwards JZ, Pulido PA, Ezzet KA, et al. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. *J Arthroplasty* 2008;23:1122-7. PMID: 18534421

115. Lieberman JR, Huo MM, Hanway J, et al. The prevalence of deep venous thrombosis after total hip arthroplasty with hypotensive epidural anesthesia. *J Bone Joint Surg Am* 1994;76:341-8. PMID: 8126039
116. Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. *J Bone Joint Surg Am* 1996;78:826-34. PMID: 8666599
117. Woolson ST, Watt JM. Intermittent pneumatic compression to prevent proximal deep venous thrombosis during and after total hip replacement. A prospective, randomized study of compression alone, compression and aspirin, and compression and low-dose warfarin. *J Bone Joint Surg Am* 1991;73:507-12. PMID: 2013589
118. Andersen BS. Postoperative activation of the haemostatic system--influence of prolonged thromboprophylaxis in patients undergoing total hip arthroplasty. *Haemostasis* 1997;27:219-27. PMID: 9690480
119. Arnesen H, Dahl OE, Aspelin T, et al. Sustained prothrombotic profile after hip replacement surgery: the influence of prolonged prophylaxis with dalteparin. *J Thromb Haemost* 2003;1:971-5. PMID: 12871363
120. Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996;335:696-700. PMID: 8703168
121. Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. *J Bone Joint Surg Am* 2001;83-A:336-45. PMID: 11263636
122. Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery--results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost* 1997;77:26-31. PMID: 9031444
123. Dahl OE, Aspelin T, Arnesen H, et al. Increased activation of coagulation and formation of late deep venous thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thromb Res* 1995;80:299-306. PMID: 8585042
124. Eriksson BI, Lassen MR, PENTasaccharide in Hip-FRActure Surgery Plus, Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2003;163:1337-42. PMID: 12796070
125. Manganelli D, Pazzagli M, Mazzantini D, et al. Prolonged prophylaxis with unfractionated heparin is effective to reduce delayed deep vein thrombosis in total hip replacement. *Respiration* 1998;65:369-74. PMID: 9782219
126. Nilsson PE, Bergqvist D, Benoni G, et al. The post-discharge prophylactic management of the orthopedic patient with low-molecular-weight heparin: enoxaparin. *Orthopedics* 1997;20:22-5. PMID: 9048404
127. Planes A, Vochelle N. The post-hospital discharge venous thrombosis risk of the orthopedic patient. *Orthopedics* 1997;20:18-21. PMID: 9048403
128. Planes A, Vochelle N, Darmon JY. Out-of-hospital prophylaxis with low-molecular-weight heparin in hip surgery: the French study--venographic outcome at 35 days. *Chest* 1998;114:125S-9S. PMID: 9726707
129. Planes A, Vochelle N, Darmon JY, et al. Efficacy and safety of postdischarge administration of enoxaparin in the prevention of deep venous thrombosis after total hip replacement. A prospective randomised double-blind placebo-controlled trial. *Drugs* 1996;52:47-54. PMID: 9042560
130. Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 1996;348:224-8. PMID: 8684199

131. Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002;162:1966-71. PMID: 12230419
132. Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med* 1989;149:771-4. PMID: 2650646
133. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, et al. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *Int Angiol* 1996;15:162-8. PMID: 8803642
134. Stannard JP, Harris RM, Bucknell AL, et al. Prophylaxis of deep venous thrombosis after total hip arthroplasty by using intermittent compression of the plantar venous plexus. *Am J Orthop* 1996;25:127-34. PMID: 8640382
135. Yokote R, Matsubara M, Hirasawa N, Hagio S, Ishii K, Takata C. Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population? *J Bone Joint Surg Br* 2011;93-B:251-6. PMID: 21282767
136. Dorr LD, Gendelman V, Maheshwari AV, et al. Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. *J Bone Joint Surg Am* 2007;89:2648-57. PMID: 18056497
137. Gandhi R, Razak F, Tso P, et al. Metabolic syndrome and the incidence of symptomatic deep vein thrombosis following total knee arthroplasty. *J Rheumatol* 2009;36:2298-301. PMID: 19684153
138. Leizorovicz A, Turpie AGG, Cohen AT, et al. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART Study. *Journal of Thrombosis and Haemostasis* 2005;3:28-34. PMID: 15634263
139. Lemos MJ, Sutton D, Hozack WJ, et al. Pulmonary embolism in total hip and knee arthroplasty. Risk factors in patients on warfarin prophylaxis and analysis of the prothrombin time as an indicator of warfarin's prophylactic effect. *Clin Orthop* 1992;158-63. PMID: 1516307
140. McNamara I, Sharma A, Prevost T, et al. Symptomatic venous thromboembolism following a hip fracture. *Acta Orthop* 2009;80:687-92. PMID: 19968601
141. Ryan DH, Crowther MA, Ginsberg JS, et al. Relation of factor V Leiden genotype to risk for acute deep venous thrombosis after joint replacement surgery. *Ann Intern Med* 1998;128:270-6. PMID: 9471929
142. Haas SB, Tribus CB, Insall JN, et al. The significance of calf thrombi after total knee arthroplasty. *J Bone Joint Surg Br* 1992;74:799-802. PMID: 1447236
143. Lieberman JR, Wollaeger J, Dorey F, et al. The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. *J Bone Joint Surg Am* 1997;79:319-25. PMID: 9070518
144. Cusick LA, Beverland DE. The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. *J Bone Joint Surg Br* 2009;91:645-8. PMID: 19407300
145. Happe LE, Farrelly EM, Stanford RH, et al. Cost and occurrence of thrombocytopenia in patients receiving venous thromboembolism prophylaxis following major orthopaedic surgeries. *J Thromb Thrombolysis* 2008;26:125-31. PMID: 18034323
146. Sachs RA, Smith JH, Kuney M, et al. Does anticoagulation do more harm than good? A comparison of patients treated without prophylaxis and patients treated with low-dose warfarin after total knee arthroplasty. *J Arthroplasty* 2003;18:389-95. PMID: 12820078
147. Shorr AF, Kwong LM, Sarnes M, et al. Venous thromboembolism after orthopedic surgery: implications of the choice for prophylaxis. *Thromb Res* 2007;121:17-24. PMID: 17449088

148. Bozic KJ, Vail TP, Pekow PS, et al. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? *J Arthroplasty* 2010;25:1053-60. PMID: 19679434
149. Froimson MI, Murray TG, Fazekas AF. Venous thromboembolic disease reduction with a portable pneumatic compression device. *J Arthroplasty* 2009;24:310-6. PMID: 18534456
150. Gerkens S, Crott R, Closon MC, Horsmans Y, Beguin C. Comparing the quality of care across Belgian hospitals from medical basic datasets: the case of the thromboembolism prophylaxis after major orthopaedic surgery. *J Eval in Clin Pract* 2010;16:685-92. PMID: 20545808
151. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg* 1999;86:992-1004. PMID: 10460633
152. Anderson DR, O'Brien BJ, Levine MN, et al. Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. *Ann Intern Med* 1993;119:1105-12. PMID: 8239230
153. Brookenthal KR, Freedman KB, Lotke PA, et al. A meta-analysis of thromboembolic prophylaxis in total knee arthroplasty. *J Arthroplasty* 2001;16:293-300. PMID: 11307125
154. Douketis JD, Eikelboom JW, Quinlan DJ, et al. Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Intern Med* 2002;162:1465-71. PMID: 12090882
155. Edmonds MJR, Crichton TJH, Runciman WB, et al. Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ J Surg* 2004;74:1082-97. PMID: 15574153
156. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001;358:9-15. PMID: 11454370
157. Eikelboom JW, Quinlan DJ, O'Donnell M. Major Bleeding, mortality, and efficacy of fondaparinux in venous thromboembolism prevention trials. *Circulation* 2009;120:2006-11. PMID: 19884469
158. Eriksson BI, Bauer KA, Lassen MR, et al. Influence of the duration of fondaparinux prophylaxis in preventing venous thromboembolism following hip fracture surgery. *The Journal of Bone and Joint Surgery (Proceedings)* 2004;86-B (SUPP_III):233-a.
159. Freedman KB, Brookenthal KR, Fitzgerald RH, Jr, et al. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am* 2000;82-A:929-38. PMID: 10901307
160. Handoll HH, Farrar MJ, McBurnie J, et al. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane database of systematic reviews (Online : Update Software)* 2002;
161. Howard AW, Aaron SD. Low molecular weight heparin decreases proximal and distal deep venous thrombosis following total knee arthroplasty. A meta-analysis of randomized trials. *Thromb Haemost* 1998;79:902-6. PMID: 9609217
162. Hu S, Zhang Z-, Hua Y-, et al. A comparison of regional and general anaesthesia for total replacement of the hip or knee: A meta-analysis. *Journal of Bone and Joint Surgery - Series B* 2009;91:935-42. PMID: 19567860
163. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001;135:858-69. PMID: 11712876
164. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA* 1994;271:1780-5. PMID: 7515115

165. Lee AY, Gent M, Julian JA, et al. Bilateral vs. ipsilateral venography as the primary efficacy outcome measure in thromboprophylaxis clinical trials: a systematic review. *J Thromb Haemost* 2004;2:1752-9. PMID: 15456486
166. Levine RL, McCollum D, Hursting MJ. How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? *Chest* 2006;130:681-7. PMID: 16963663
167. McCart GM, Kayser SR. Therapeutic equivalency of low-molecular-weight heparins. *Ann Pharmacother* 2002;36:1042-57. PMID: 12022908
168. Mismetti P, Laporte S, Zufferey P, et al. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: A meta-analysis. *Journal of Thrombosis and Haemostasis* 2004;2:1058-70. PMID: 15219187
169. Mohr DN, Silverstein MD, Murtaugh PA, et al. Prophylactic agents for venous thrombosis in elective hip surgery. Meta-analysis of studies using venographic assessment. *Arch Intern Med* 1993;153:2221-8. PMID: 8215725
170. Muntz J, Scott DA, Lloyd A, et al. Major bleeding rates after prophylaxis against venous thromboembolism: Systematic review, meta-analysis, and cost implications. *Int J Technol Assess Health Care* 2004;20:405-14. PMID: 15609788
171. Murray DW, Britton AR, Bulstrode CJ. Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg Br* 1996;78:863-70. PMID: 8950998
172. Ning N, Chen H-, Chen Z-. Intermittent pneumatic compression for deep venous thrombosis prevention after major orthopedic operation: A systematic review. *Chinese Journal of Evidence-Based Medicine* 2010;10:471-5.
173. Nutescu EA, Shapiro NL, Feinstein H, et al. Tinzaparin: Considerations for Use in Clinical Practice. *Ann Pharmacother* 2003;37:1831-40. PMID: 14632588
174. O'Donnell M, Linkins LA, Kearon C, et al. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2003;163:1362-6. PMID: 12796074
175. Sharrock NE, Gonzalez Della Valle A, Go G, et al. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop* 2008;466:714-21. PMID: 18264861
176. Slobogean GP, Lefaivre KA, Nicolaou S, et al. A systematic review of thromboprophylaxis for pelvic and acetabular fractures. *J Orthop Trauma* 2009;23:379-84. PMID: 19390367
177. Smith TO, Hing CB. Is a tourniquet beneficial in total knee replacement surgery?. A meta-analysis and systematic review. *Knee* 2010;17:141-7. PMID: 19616954
178. Strebel N, Prins M, Agnelli G, et al. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med* 2002;162:1451-6. PMID: 12090880
179. Tasker A, Harbord R, Bannister G. Meta-analysis of low molecular weight heparin versus placebo in patients undergoing total hip replacement and post-operative morbidity and mortality since their introduction. *HIP International* 2010;20:64-74. PMID: 20383852
180. Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002;162:1833-40. PMID: 12196081
181. Westrich GH, Haas SB, Mosca P, et al. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. *J Bone Joint Surg Br* 2000;82:795-800. PMID: 10990299

182. Wolowacz SE, Roskell NS, Plumb JM, et al. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009;101:77-85. PMID: 19132192
183. Xing KH, Morrison G, Lim W, et al. Has the incidence of deep vein thrombosis in patients undergoing total hip/knee arthroplasty changed over time? A systematic review of randomized controlled trials. *Thromb Res* 2008;123:24-34. PMID: 18620740
184. Zufferey P, Laporte S, Quenet S, et al. Optimal low-molecular-weight heparin regimen in major orthopaedic surgery: A meta-analysis of randomised trials. *Thromb Haemost* 2003;90:654-61. PMID: 14515186
185. Friedman RJ, Dahl OE, Rosencher N, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res* 2010;126:175-82. PMID: 20434759
186. Cohen AT, Bailey CS, Alikhan R, et al. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty--a meta-analysis. *Thromb Haemost* 2001;85:940-1. PMID: 11372694
187. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet* 1992;340:152-8. PMID: 1352573
188. Leizorovicz A, Haugh MC, Chapuis F, et al. Low Molecular Weight Heparin In Prevention Of Perioperative Thrombosis. *BMJ* 1992;305:913-20. PMID: 1281030
189. Turpie AG, bauer KA, Eriksson BI, et al. Superiority of fondaparinux over enoxaparin in preventing venous thromboembolism in major orthopedic surgery using different efficacy end points. *Chest* 2004;126:501-8. PMID: 15302737
190. Dahl OE, Quinlan DJ, Bergqvist D, Eikelboom JW. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemost* 2010;8:1966-75. PMID: 20586919
191. Michot M, Conen D, Holtz D, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low-molecular weight heparin. *Arthroscopy* 2002;18:257-63. PMID: 11877611
192. Lapidus LJ, Rosfors S, Ponzer S, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma* 2007;21:52-7. PMID: 17211270
193. Ettema HB, Kollen BJ, Verheyen CC, et al. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost* 2008;6:1093-8. PMID: 18429944
194. Testroote M, Stigter W, de Visser DC, et al. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev* 2008;:006681. PMID: 18843725
195. Ramos J, Perrotta C, Badariotti G, et al. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database Syst Rev* 2008;:005259. PMID: 18843687
196. Ramos J, Perrotta C, Badariotti G, et al. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database Syst Rev* 2007;:005259. PMID: 17443578
197. Planes A, Vochelle N, Fagola M, et al. Prevention of deep vein thrombosis after total hip replacement. The effect of low-molecular-weight heparin with spinal and general anaesthesia. *J Bone Joint Surg Br* 1991;73:418-22. PMID: 1670442

198. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty--the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res* 1998;89:281-7. PMID: 9669750
199. Xarelto. Xarelto. Available at: <http://www.xareltohcp.com/>. Accessed July, 2011.
200. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75. PMID: 18579811
201. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9. PMID: 18582928
202. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AGG. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86. PMID: 18579812
203. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty: a randomised trial. *Lancet* 2009;373:1673-80. PMID: 19411100

Appendix A. Search Strategy

Search one and search two were originally conducted in July 2010 and were both updated, following the same methodology, in May 2011.

Search 1: Major orthopedic surgery

Medline and Cochrane Central Register of Controlled Trials (OVID)

1. arthroplasty, replacement, knee/
2. knee.mp AND arthroplasty/
3. total knee replacement.mp
4. knee arthroplasty.mp
5. TKR.mp
6. knee prosthesis/
7. knee prosthesis.mp
8. knee joint.mp
9. arthroplasty, replacement, hip/
10. hip.mp AND arthroplasty/
11. total hip replacement.mp
12. hip arthroplasty.mp
13. THR.mp
14. hip prosthesis/
15. hip prosthesis.mp
16. hip fracture surgery.mp
17. HFS.mp
18. hip.mp AND fracture fixation, internal/
19. or/1-18
20. pulmonary embolism/
21. pulmonary embol*.mp
22. pulmonary thromboembol*.mp
23. PE.mp
24. deep vein thrombos*.mp
25. deep venous thrombos*.mp
26. deep venous thromboembol*.mp
27. deep vein thromboembol*.mp
28. DVT.mp
29. venous thromboembolism/
30. venous thromboembol*.mp
31. VTE.mp
32. venous thrombosis/
33. venous thrombos*.mp
34. clot.mp
35. or/20-34
36. anticoagulants/
37. aspirin/
38. aspirin.mp
39. clopidogrel.mp
40. ticlopidine.mp
41. prasugrel.mp

42. heparin/
43. heparinoids/
44. heparin.mp
45. UFH.mp
46. heparin, low-molecular weight/
47. low molecular weight heparin.mp
48. LMWH.mp
49. enoxaparin.mp
50. dalteparin.mp
51. nadroparin.mp
52. ardeparin.mp
53. bemiparin.mp
54. certoparin.mp
55. parnaparin.mp
56. reviparin.mp
57. tinzaparin.mp
58. danaparoid.mp
59. fondaparinux.mp
60. idraparinux.mp
61. rivaroxaban.mp
62. hirudins/
63. desirudin.mp
64. argatroban.mp
65. bivalirudin.mp
66. lepirudin.mp
67. dabigatran.mp
68. warfarin/
69. 4-Hydroxycoumarins/
70. warfarin.mp
71. acenocoumarol.mp
72. dicoumarol.mp
73. dextran sulfate/
74. dextran sulfate.mp
75. or/36-74
76. stockings, compression/
77. compression stocking.mp
78. compression stockings.mp
79. compression boot.mp
80. graduated compression stocking.mp
81. graduated compression stockings.mp
82. elastic stocking.mp
83. elastic stockings.mp
84. graduated compression stocking.mp
85. graduated compression stockings.mp
86. GCS.mp
87. venous foot pump.mp

88. VFP.mp
89. intermittent pneumatic compression devices/
90. intermittent pneumatic compression.mp
91. pneumatic compression stocking.mp
92. pneumatic compression stockings.mp
93. pneumatic hose.mp
94. pneumatic compression hose.mp
95. IPC.mp
96. or/76-95
97. vena cava filters/
98. vena cava filter.mp
99. vena cava filters.mp
100. IVC.mp
101. or/97-100
102. 75 or 96 or 101
103. 19 and 35 and 102

Scopus

((((ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin OR parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin OR lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (((((ALL(compression stocking\$)) OR (ALL(graduated compression stocking\$)) OR (ALL(elastic stocking\$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)))) OR (ALL(pneumatic compression)))))) AND (((((ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)) OR (ALL(venous thromboembol*)) OR (ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*))) OR (((ALL(venous thromboembol*)) OR (ALL(pulmonary thromboembol*)) OR (ALL(pulmonary embol*)) OR (ALL(venous thrombos*)))))) AND (((ALL(knee replacement)) OR (ALL(knee arthroplasty)) OR (ALL(hip arthroplasty)) OR (ALL(hip replacement)) OR (ALL(hip fracture surgery))))))

Search 2: Other orthopedic surgery

Medline and Cochrane Central Register of Controlled Trials (OVID)

1. knee arthroscop*
2. arthroscop* adj knee
3. meniscectomy ADJ arthroscop*
4. synovectomy ADJ arthroscop*
5. cruciate ligament AND (arthroscop* OR repair)
6. casts, surgical/ OR casts, surgical.mp
7. plaster cast.mp
8. splint*.mp OR splints/
9. Achilles ADJ tendon

10. tibial plateau fracture.mp
11. distal ADJ femur fracture.mp
12. lumbar ADJ laminectomy.mp
13. lumbar ADJ discectomy.mp
14. lumbar ADJ spinal fusion.mp
15. (fracture fixation, internal/ OR fracture fixation, intramedullary/) AND (femur OR femor*
OR tibia* OR ankle OR foot)
16. osteotomy.mp AND (femur OR femor* OR tibia*)
17. or/1-16
18. anticoagulants/
19. aspirin/
20. aspirin.mp
21. clopidogrel.mp
22. ticlopidine.mp
23. prasugrel.mp
24. heparin/
25. heparinoids/
26. heparin.mp
27. UFH.mp
28. heparin, low-molecular weight/
29. low molecular weight heparin.mp
30. LMWH.mp
31. enoxaparin.mp
32. dalteparin.mp
33. nadroparin.mp
34. ardeparin.mp
35. bemiparin.mp
36. certoparin.mp
37. parnaparin.mp
38. reviparin.mp
39. tinzaparin.mp
40. danaparoid.mp
41. fondaparinux.mp
42. idraparinux.mp
43. rivaroxaban.mp
44. hirudins/
45. desirudin.mp
46. argatroban.mp
47. bivalirudin.mp
48. lepirudin.mp
49. dabigatran.mp
50. warfarin/
51. 4-Hydroxycoumarins/
52. warfarin.mp
53. acenocoumarol.mp
54. dicoumarol.mp

55. dextran sulfate/
56. dextran sulfate.mp
57. or/18-56
58. stockings, compression/
59. compression stocking.mp
60. compression stockings.mp
61. compression boot.mp
62. graduated compression stocking.mp
63. graduated compression stockings.mp
64. elastic stocking.mp
65. elastic stockings.mp
66. graduated compression stocking.mp
67. graduated compression stockings.mp
68. GCS.mp
69. venous foot pump.mp
70. VFP.mp
71. intermittent pneumatic compression devices/
72. intermittent pneumatic compression.mp
73. pneumatic compression stocking.mp
74. pneumatic compression stockings.mp
75. pneumatic hose.mp
76. pneumatic compression hose.mp
77. IPC.mp
78. or/58-77
79. pulmonary embolism/
80. pulmonary embol*.mp
81. pulmonary thromboembol*.mp
82. PE.mp
83. deep vein thrombos*.mp
84. deep venous thrombos*.mp
85. deep venous thromboembol*.mp
86. deep vein thromboembol*.mp
87. DVT
88. venous thromboembolism/
89. venous thromboembol*.mp
90. VTE
91. venous thrombosis/
92. venous thrombos*.mp
93. clot.mp
94. or/79-93
95. 57 or 78
96. 17 and 94 and 95

Scopus

(((((lumbar PRE/1 spinal fusion) OR (lumbar PRE/1 diskectomy) OR (lumbar PRE/1 laminectomy) OR (open reduction internal fixation PRE/1 ankle) OR (open reduction internal fixation PRE/1 foot))) OR (((open reduction internal fixation PRE/1 tibia*) OR (open reduction internal fixation PRE/1 femur*) OR (osteotomy PRE/1 femur*) OR (osteotomy PRE/1 tibia*) OR (distal PRE/1 femur* fracture) OR (tibial plateau fracture) OR (intermedullary fixation)))))) AND (((((ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)) OR (ALL(venous thromboembol*)) OR (ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)))) OR (((ALL(venous thromboembol*)) OR (ALL(pulmonary thromboembol*)) OR (ALL(pulmonary embol*)) OR (ALL(venous thrombos*))))))

Appendix B. Data Extraction Form

VTE Prophylaxis in Orthopedic Surgery CER Key Questions 1, 3-9

STUDY IDENTIFICATION

Unique ID:	First author's name, publication year:	Study acronym (if applicable):	Publication format: <input type="checkbox"/> Full text manuscript <input type="checkbox"/> Abstract <input type="checkbox"/> Other (specify):
Funding Source (specify): <input type="checkbox"/> Industry <input type="checkbox"/> Government/Foundation <input type="checkbox"/> Academia <input type="checkbox"/> Other/Unknown		Geographic location:	Number of Centers:
			Total N randomized (N randomized in arms we use):

STUDY DESIGN AND QUALITY CHARACTERISTICS

(Select either RCT or observational and complete corresponding section, if you answer N report why)

<input type="checkbox"/> Randomized controlled trial	
Were the groups similar baseline in terms of baseline characteristics? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Were outcomes assessed using a valid methodology and criteria? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>
Were subjects and providers blind to intervention status of participants? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Were outcome assessors blind to intervention status? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>
Randomization technique described:	Outcome assessment described:
Was intention to treat analysis used? Y <input type="checkbox"/> N <input type="checkbox"/>	
Were methods used for randomization adequate? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Was incomplete data adequately addressed? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>
Was allocation concealment adequate? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Conflicts of interest reported and insignificant? Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>
Was the differential loss to followup between groups	Was the overall loss to followup <20%?

<10%? Y <input type="checkbox"/> N <input type="checkbox"/>		Y <input type="checkbox"/> N <input type="checkbox"/>	
Duration of followup (longest):		Followup % for the primary outcome: Intervention Comparator	
Overall quality score (use protocol for criteria): good <input type="checkbox"/> fair <input type="checkbox"/> poor <input type="checkbox"/>			
<input type="checkbox"/> Controlled observational study (specify design in detail):			
Unbiased selection of cohort: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Selection minimizes baseline differences: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Blinded outcome assessment: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Outcome assessment described:
Sample size calculated: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Adequate description of cohort: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Validated method to ascertain exposure: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Validated method to ascertain outcomes: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>
Adequate followup period: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Completeness of followup: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Adequate analysis to control for confounding: Y <input type="checkbox"/> N <input type="checkbox"/> Partially <input type="checkbox"/> Can't tell <input type="checkbox"/>	Covariates/potential confounders adjusted for:
Overall quality score (use protocol for criteria): good <input type="checkbox"/> fair <input type="checkbox"/> poor <input type="checkbox"/>			

Diagnosis of DVT and PE

(describe protocol including diagnostic tests, timing, if symptoms were required for screening)

DVT	<input type="checkbox"/> Venography <input type="checkbox"/> Ultrasound <input type="checkbox"/> Other:
PE	<input type="checkbox"/> Angiography <input type="checkbox"/> CT scan <input type="checkbox"/> Other: <input type="checkbox"/> VQ Scan plus [<input type="checkbox"/> PLOPED <input type="checkbox"/> Biello et al. <input type="checkbox"/> Clinical suspicion]

PATIENT POPULATION

<p>Surgical procedure (If more than 1 of the three surgeries please indicate n/N (%) for each surgery):</p> <p><input type="checkbox"/> Total hip replacement <input type="checkbox"/> Total knee replacement <input type="checkbox"/> Hip fracture surgery</p> <p>Surgical procedure (If more than 1 of the three surgeries please indicate n/N (%) for each surgery):</p> <p><input type="checkbox"/> Knee arthroscopy <input type="checkbox"/> Elective spine surgery Specify types of surgeries included: Specify types of surgeries included:</p> <p><input type="checkbox"/> Surgical repair of lower extremity injury distal to the hip Specify types of surgeries included:</p>

Inclusion criteria:	Exclusion criteria:
----------------------------	----------------------------

STUDY INTERVENTION

- ☐ Pharmacologic agent versus placebo
 ☐ Mechanical agent versus placebo
☐ Pharmacologic agent versus pharmacologic agent
 ☐ Mechanical agent versus mechanical agent
☐ Pharmacologic agent versus mechanical agent
 ☐ Mechanical agent versus IVC filter
☐ Pharmacologic agent versus pharmacological + mechanical agents (or vice versa)*
 ☐ Others (SPECIFY)
☐ Prolonged versus standard duration pharmacological prophylaxis

*When combination therapy is compared to a mono-therapy, indicate in the box below which interventions are working as a combination therapy.

Please specify the intervention(s) below:

<u>Intervention 1</u>	<u>Intervention 2</u>	<u>Intervention 3</u>	<u>Intervention 4</u>
	Placebo <input type="checkbox"/>	Placebo <input type="checkbox"/>	Placebo <input type="checkbox"/>
Pharmacologic Class:	Pharmacologic Class:	Pharmacologic Class:	Pharmacologic Class:
Drug name:	Drug name:	Drug name:	Drug name:
Dose:	Dose:	Dose:	Dose:
Route:	Route:	Route:	Route:
Frequency:	Frequency:	Frequency:	Frequency:
Timing of first dose:	Timing of first dose:	Timing of first dose:	Timing of first dose:
Duration of therapy (no. days):	Duration of therapy (no. days):	Duration of therapy (no. days):	Duration of therapy (no. days):
Other (ex. INR goals):	Other (ex. INR goals):	Other (ex. INR goals):	Other (ex. INR goals):
<u>Mechanical Intervention</u> Product name:	<u>Mechanical Intervention</u> Product name	<u>Mechanical Intervention</u> Product name:	<u>Mechanical Intervention</u> Product name:
Initiation relative to surgery:	Initiation relative to surgery:	Initiation relative to surgery:	Initiation relative to surgery:

Duration applied /d:	Duration applied /d:	Duration applied /d:	Duration applied /d:
Total duration of therapy:	Total duration of therapy:	Total duration of therapy:	Total duration of therapy:
<u>Inferior vena cava filter intervention</u> Device name:	<u>Inferior vena cava filter intervention</u> Device name:	<u>Inferior vena cava filter intervention</u> Device name:	<u>Inferior vena cava filter intervention</u> Device name:

CONCURRENT STANDARD THERAPIES / INTERVENTIONS
(therapies which were given to all patients regardless of arm to which they were randomized)

Concurrent mechanical (e.g. stockings):	Mobilization regimen:	Concurrent medications:
Other:		

PATIENT CHARACTERISTICS

Characteristic	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Number of participants (N)				
Age (mean±SD, median IQR)				
Females n/N (%)				
Race n/N (%)				
• White				
• Black				
• Hispanic				
• Asian				
• Other				
Weight (mean ± SD, range)				
BMI (mean ± SD, range)				
Smoker n/N (%)				
Obesity n/N (%)				
History of VTE n/N (%)				

Characteristic	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Varicosity n/N (%)				
Estrogen intake n/N (%)				
Diabetes n/N (%)				
Cancer n/N (%)				
CHF n/N (%)				
COPD n/N (%)				
CVD n/N (%)				
Previous orthopedic surgery n/N (%)				
Multiple risk factors present (3+ or specify) n/N (%)				

SURGICAL CHARACTERISTICS

Characteristic	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Primary surgery n/N (%)				
Revision surgery n/N (%)				
Cemented fixation n/N (%)				
Tourniquet use n/N (%)				
Anterolateral approach n/N (%)				
Posteriolateral approach n/N (%)				
Autologous blood transfusion n/N (%)				
Duration of surgery in min (mean \pm SD, range)				
Duration of anesthesia in min (mean \pm SD, range)				
General anesthesia n/N (%)				
Regional anesthesia n/N (%)				
General and regional				

Characteristic	Intervention 1	Intervention 2	Intervention 3	Intervention 4
anesthesia n/N (%)				
Hospital LOS Mean (SD)				

FINAL HEALTH OUTCOMES (report both n/N (%) and hazard ratios when available for all outcomes)

Outcome	Definition	Time point	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Symptomatic objectively confirmed VTE						
Major VTE (proximal DVT, non-fatal PE, or VTE related mortality)						
Fatal PE						
Non-fatal PE						
PE not otherwise specified (fatal or not)						
Post-thrombotic syndrome						
Mortality due to bleeding						
Total Mortality						
Health related QOL Scale:						

INTERMEDIATE HEALTH OUTCOMES (report both n/N (%) and hazard ratios when available for all outcomes)

Outcome	Definition	Time point	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Total DVT (asymptomatic, symptomatic, distal, or proximal)						
Asymptomatic DVT						
Symptomatic DVT						
Proximal DVT						
Distal DVT						

ADVERSE OUTCOMES (report both n/N (%) and hazard ratios when available for all outcomes)

Outcome	Definition	Time point	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Major bleeding						
Minor bleeding						
Major bleeding leading to re-operation						
Surgical site bleeding						
Bleeding leading to infection						
Bleeding leading to transfusion						
Heparin-induced thrombocytopenia						
Discomfort						
Re-admission						
Re-operation						
IVC filter placement-associated insertion site thrombosis						

Does This trial or study have sub group analysis looking at age, gender and ethnicity? ☐ Yes ☐ No

If yes, report data:

Does this trial or study have information that might be used to answer

KQ2?

KQ1?

KQ3?

If yes, please print a copy of the article and put into the correct pile for KQ1, 2 or 3.

Appendix C. Excluded Studies From Full-Text Review

Table 1. Excluded studies at the full text level from search one

Excluded as a duplicate publication (n=21)	
1.	Anders JO, Fuhrmann R, Roth A, et al. How can we decrease the number of thrombosis and pulmonary embolism in total hip replacement? <i>Z Orthop Ihre</i> 2004;142:328-32.
2.	Banssillon V, Dejour H, Besson L, et al. Prevention of deep venous thromboses (DVT) in orthopaedic surgery for total hip replacement (THR). Randomised dose-ranging trial. <i>ANN-CHIR</i> 1987;41:377-85.
3.	Bergqvist D, Breddin K, Ten Cate JW, et al. Thromboprophylaxis in hip fracture surgery: A pilot study comparing danaparoid, enoxaparin and dalteparin. <i>Haemostasis</i> 1999;29:310-7.
4.	Camporese G, Bernardi E, Prandoni P, et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. <i>Ann Intern Med</i> 2008;149:73-82.
5.	Enyart JJ, Jones RJ. Low-dose warfarin for prevention of symptomatic thromboembolism after orthopedic surgery. <i>Ann Pharmacother</i> 2005;39:1002-7.
6.	Friksson BI, Ekman S, Lindbratt S, et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (revase) with Thai of unfractionated heparin in patients having a total hip replacement. <i>Journal of Bone and Joint Surgery - Series A</i> 1997;79:326-33.
7.	Handoll HH, Farrar MJ, McBirnie J, et al. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. <i>Cochrane database of systematic reviews (Online : Update Software)</i> 2000.
8.	Kakkar AK, Brenner B, Dahl OE, et al. <i>Lancet</i> 2008;372:31-9.
9.	Kim YH, Choi IY, Park MR, et al. Deep vein thrombosis after uncemented total hip replacement. <i>Bull Hosp Jt Dis</i> 1997;56:133-9.
10.	Lassen MR, Ageno W, Borris LC, et al. <i>N Engl J Med</i> 2008;358:2776-86.
11.	Navarro-Quilis A, Castellet E, Rocha E, et al. Efficacy and safety of bemiparin compared with enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind clinical trial. <i>J Thromb Haemost</i> 2003;1:425-32.
12.	Palement GD, Wessinger SJ, Walter AC, et al. Low dose warfarin versus external pneumatic compression against venous thromboembolism following total hip replacement. <i>J Arthroplasty</i> 1987;2:23-6.
13.	Patel A, Couband D, Feron JM, et al. Prevention of deep venous thrombosis in arthroplastic surgery of the hip by the combination of heparinotherapy and the antithrombosis stocking. <i>Presse medicale (Paris)</i> 1983;France.
14.	Planes A, Vochelle N, Mazas F, et al. Enoxaparin versus standard heparin in the prophylaxis of deep vein thrombosis after total hip replacement: A double-blind randomized trial. <i>Rev Med Interne</i> 1988;9:327-33.
15.	Rader CP, Kramer C, Hendrich C, et al. Experiences with an ankle joint moving device in thromboprophylaxis after total knee arthroplasty. <i>Z Orthop Ihre</i> 1998;136:467-70.
16.	RE-MOBILIZE Writing C, Ginsberg JS, Davidson BL, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. <i>J Arthroplasty</i> 2009;24:1-9.
17.	Sevestre MA, Labarere J, Brin S, et al. Optimizing history taking for evaluating the risk of venous thromboembolism: The OPTIMEV study. <i>J Mal Vasc</i> 2005;30:217-27.
18.	The German Hip Arthroplasty Trial, Group. Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement. <i>Arch Orthop Trauma Surg</i> 1992;111:110-20.
19.	Tian H, Song F, Zhang K, et al. Efficacy and safety of aspirin in prevention of venous thromboembolism after total joint arthroplasty. <i>National Medical Journal of China</i> 2007;87:3349-52.
20.	Turpie AG, Lassen MR, Davidson BL, et al. <i>Lancet</i> 2009;373:1673-80.
21.	Welin-Berger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. <i>Acta Orthop Scand</i> 1982;53:937-45.
Excluded as a publication prior to 1980 (n=4)	
22.	Hull RD, Raskob GE, Gent M, et al. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. <i>J Am Med Assoc</i> 1990;263:2313-7.
23.	Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein

thrombosis in patients undergoing post-traumatic hip surgery. *Acta Chir Scand* 1980;146:319-22.

24. Paiement GD, Schutzer SF, Wessinger SJ, et al. Influence of prophylaxis on proximal venous thrombus formation after total hip arthroplasty. *J Arthroplasty* 1992;7:471-5.

25. Sarmiento A, Goswami AD. Thromboembolic prophylaxis with use of aspirin, exercise, and graded elastic stockings or intermittent compression devices in patients managed with total hip arthroplasty. *J Bone Joint Surg Am* 1999;81:339-46.

Excluded because citation was not a full text systematic review, study or trial (n=196)

26. Abdool-Carrim T, Adler H, Becker P, et al. The cost and benefit of prophylaxis against deep vein thrombosis in elective hip replacement. *DVT/PE Prophylaxis Consensus Forum. SAMJ, S Afr med j* 1997;87:594-600.

27. Adequate prophylaxis reduces deaths from venous thromboembolism. *Drugs and Therapy Perspectives* 1996;8:11-3.

28. Agnelli G, Cimminiello C. Prevention of venous thromboembolism in orthopedic surgery and traumatology. *Recenti Prog Med* 2007;98:25S-32S.

29. Agnelli G, Sonaglia F. Clinical status of direct thrombin inhibitors. *Crit Rev Oncol* 1999;31:97-117.

30. Agudelo JF, Morgan SJ, Smith WR. Venous thromboembolism in orthopedic trauma patients. *Orthopedics* 2005;28:1164-71.

31. Ahmed A. Prevention of deep vein thrombosis and pulmonary embolism in the perioperative period: A review. *Journal of the Pakistan Medical Association* 2005;55:343-7.

32. Alexander P, Giangola G. Deep venous thrombosis and pulmonary embolism: Diagnosis, prophylaxis, and treatment. *Ann Vasc Surg* 1999;13:318-27.

33. Alhenc-Gelas M. Heparin induced thrombocytopenia: Is it over? *Revue Francophone des Laboratoires* 2008;38:12-4.

34. Anbar M. Shifting from phenomenological thermography to pathophysiology based thermal imaging. *IEEE Engineering in Medicine and Biology Magazine* 1998;17:25-33.

35. Andreozzi GM, Mannucci P, Nuzzaci G, et al. Linee-guida per la diagnosi e il trattamento della trombosi venosa profonda. *Minerva Cardioangiol* 2000;48:201-75.

36. Annemans L, Minjoulat-Rey MC, De Knock M, et al. Cost consequence analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery in Belgium. *Acta Clin Belg* 2004;59:346-57.

37. Archibeck MJ, White Jr. RE. What's new in adult reconstructive knee surgery. *Journal of Bone and Joint Surgery - Series A* 2005;87:1656-66.

38. Ardeparin and danaparoid for prevention of deep vein thrombosis. *Med Lett Drugs Ther* 1997;39:94-5.

39. Arora VM, McGory ML, Fung CH. Quality indicators for hospitalization and surgery in vulnerable elders. *J Am Geriatr Soc* 2007;55.

40. Barrellier MT. Thromboprophylaxis and total hip replacement: A cost-efficacy study comparing duplex screening of asymptomatic venous thrombosis versus prolonged prophylaxis with low-molecular-weight heparins. *Phlebology* 2002;17:93-7.

41. Bauer KA, Eriksson BI, Lassen MR, et al. Influence of the duration of fondaparinux prophylaxis in preventing venous thromboembolism following hip fracture surgery. *Blood* 2002;100.

42. Berger R. Comparing options for preventing PE: Pneumatic compression vs anticoagulation. *J Crit Illn* 2001;16:9-11.

43. Bergqvist D. Inferior vena cava filters. *World J Surg* 2007;31:265-6.

44. Bergqvist D, Jonsson B. Cost-effectiveness of prolonged out-of-hospital prophylaxis with low-molecular-weight heparin following total hip replacement. *Haemostasis* 2000;30:130-5.

45. Berry DJ. DVT prophylaxis after THA is safe and effective. *Orthopedics* 2000;23:1028-30.

46. Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis. *Am J Cardiovasc Drugs* 2005;5:121-30.

47. Borris LC, Hauch O, Jorgensen LN, et al. Low molecular weight heparin (Enoxaparin) versus Dextran 70 in the prevention of postoperative deep vein thrombosis after total hip replacement: A Danish multicenter study [Abstract]. *Acta Orthop Scand* 1990;61:52.

48. Borris LC, Petersen MB, Lassen MR. Prevention of thrombosis in hip alloplasty. *Ugeskr Laeger* 2001;163:934-5.

49. Botteman MF, Caprini J, Stephens JM, et al. Results of an economic model to assess the cost-effectiveness of

enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States. *Clin Ther* 2002;24:1960-86.

50. Bouee S, Zufferey P, Fagnani F. Budget impact analysis of Pradaxa thromboprophylaxis after total hip or total knee replacement. *Therapie* 2009;64:249-57.

51. Brand RA. 50 Years ago in CORR: Postspinal anesthesia osteomyelitis of the lumbar spine P. L. Day MD and J. J. Hinchey MD *CORR* 1958;11:185-193. *Clin Orthop* 2008;466:1755-6.

52. Capri S, Ageno W, Imberti D, et al. Extended prophylaxis of venous thromboembolism with fondaparinux in patients undergoing major orthopaedic surgery in Italy: A cost-effectiveness analysis. *Internal and Emergency Medicine* 2010;5:33-40.

53. Caprini JA, Arcelus JJ, Kudrna JC, et al. Cost-effectiveness of venous thromboembolism prophylaxis after total hip replacement. *Phlebology* 2002;17:126-33.

54. Chard R. Perioperative prevention of deep vein thrombosis. *AORN J* 2009;90:119-20.

55. Chard R, Maxwell-Downing D, Mitchell S, et al. The Best of Clinical Issues. *AORN J* 2009;90.

56. Cheng JW. Fondaparinux: a new antithrombotic agent. *Clin Ther* 2002;24:1757-69.

57. Chesser TJS, Hammett RB, Norton SA. Orthopaedic trauma in the obese patient. *Injury* 2010;41:247-52.

58. Chilov MN, Cameron ID, March LM. Evidence-based guidelines for fixing broken hips: An update. *Med J Aust* 2003;179:489-93.

59. Clagett GP, Anderson Jr. FA, Geerts W, et al. Prevention of venous thromboembolism. *Chest* 1998;114.

60. Clagett GP, Anderson Jr. FA, Levine MN, et al. Prevention of venous thromboembolism. *Chest* 1992;102.

61. Cohen AT, Hirst C, Sherrill B, et al. Meta-analysis of trials comparing ximelagatran with low molecular weight heparin for prevention of venous thromboembolism after major orthopaedic surgery. *Br J Surg* 2005;92:1335-44.

62. Colwell Jr. CW. Dosing and timing of low-molecular-weight heparin thromboprophylaxis in total hip arthroplasty. *Orthopedics* 2003;26:1155-61.

63. Colwell CW, Jr. Consortium data: comparative efficacy of low molecular weight heparin and warfarin following total hip replacement. *Orthopedics* 1995;18:21-3.

64. Colwell CW. DVT prevention: Mobile compression device vs low-molecular-weight heparin. *Orthopedics* 2010;33.

65. Colwell CW, Jr, Paiement G, Pellegrini VD, Jr, et al. Advances in the prevention of venous thromboembolic disease in orthopaedics: the introduction of LMWH. *Contemp Orthop* 1993;27:551-77.

66. Crutcher J, Stickney J, Miller B. Comparison of enoxaparin and warfarin for prevention of DVT after total hip arthroplasty [Abstract]. *Orthopaedic Transactions* 1997;21:693.

67. Cushner F. Deep vein thrombosis - Concepts and controversy. *Orthopedics* 2008;31.

68. Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. *J Thromb Haemost* 2003;1:896-906.

69. Dalen JE. Pulmonary embolism: what have we learned since virchow: natural history, pathophysiology, and diagnosis. *Chest* 2002;122:1440-1456.

70. Dalen JE. Pulmonary embolism: What have we learned since virchow? Treatment and prevention. *Chest* 2002;122:1801-17.

71. Davies RR, Coady MA, Hammond GL, et al. Low molecular weight heparin: An evaluation of current and potential clinical utility in surgery. *International Journal of Angiology* 1999;8:203-15.

72. Detournay B, Planes A, Vochelle N, et al. Cost effectiveness of a low-molecular-weight heparin in prolonged prophylaxis against deep vein thrombosis after total hip replacement. *Pharmacoeconomics* 1998;13:81-9.

73. Devlin JW, Petitta A, Shepard AD, et al. Cost-effectiveness of enoxaparin versus low-dose heparin for prophylaxis against venous thrombosis after major trauma. *Pharmacotherapy* 1998;18:1335-42.

74. Dihydroergotamine/heparin in the prevention of deep-vein thrombosis after total hip replacement. *J Bone Joint Surg Am* 1989;71:311-2.

75. Dobesh PP. Novel concepts: emerging data and the role of extended prophylaxis following hip fracture surgery. *Am J Health-Syst Pharm* 2003;60:S15-9.

76. Dranitsaris G, Stumpo C, Smith R, et al. Extended dalteparin prophylaxis for venous thromboembolic events: cost-utility analysis in patients undergoing major orthopedic surgery. *Am J Cardiovasc Drugs* 2009;9:45-58.

77. Eikelboom JW, Weitz JJ. New oral anticoagulants for thromboprophylaxis in patients having hip or knee arthroplasty. *BMJ* 2011;342:7270.

78. Enneking FK, Chan V, Greger J, et al. Lower-extremity peripheral nerve blockade: Essentials of our current understanding. *Reg Anesth Pain Med* 2005;30:4-35.
79. Eriksson B. The PENTHIFRA study: Comparison of the first synthetic Factor Xa inhibitor with low molecular weight heparin (LMWH) for the prevention of venous thromboembolism (VTE) after hip fracture surgery. *Blood* 2000;96:-Abstract.
80. Eriksson BI. A multicenter, randomized, placebo-controlled, double-blind study of fondaparinux for the prolonged prevention of venous thromboembolism in hip fracture surgery. Abstracts of the Sicot/Sirot XXII World Congress 2002;318p.
81. Eriksson BI, Dahl OE, van Dijk CN, et al. A New Oral Anticoagulant, Dabigatran Etxilate, Is Effective and Safe in Preventing Venous Thromboembolism after Total Knee Replacement Surgery (The RE-MODEL Trial) [abstract]. *Blood* 2006;108:173.
82. Eriksson BI, Eriksson E, Wadenvik H, et al. Comparison of low molecular weight heparin and unfractionated heparin in prophylaxis of deep vein thrombosis and pulmonary embolism in total hip replacement. *Thromb Haemost* 1989;62:470-Abstract.
83. Eriksson BI, Lassen MR. Consistency of efficacy of extended thromboprophylaxis with fondaparinux (Arixtra) in prevention of venous thromboembolism (VTE) after hip fracture surgery according to different composite efficacy endpoints: the PENTHIFRA-PLUS study. *Journal of Thrombosis & Haemostasis* 2003;1:Abstract.
84. Fitzgerald RH,Jr. Preventing DVT following total knee replacement: a review of recent clinical trials. *Orthopedics* 1995;18:10-1.
85. Fordyce MJF, Ling RSM. The prevention of deep vein thrombosis following total hip replacement by use of the A-V impulse system: Artificial stimulation of the physiological venous foot pump [Abstract]. *Journal of Bone and Joint Surgery - British Volume* 1992;74 Suppl 2:156-7.
86. Francis CW, Pellegrini Jr. VD, Leibert KM, Totterman S, Azodo MV, Harris CM, Cox C,Marder V.J. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. *Thromb Haemost* 1995;73:1105-Abstract.
87. Francis C, Pellegrini V, Marder V, et al. A prospective clinical and economic comparison of warfarin and dalteparin in prevention of deep vein thrombosis following total hip replacement. *Journal of Vascular Surgery* 1997;Issue:O1577.
88. Friedman RJ, Caprini JA, Comp PC, et al. Dabigatran etexilate versus enoxaparin in preventing venous thromboembolism following total knee arthroplasty [abstract no:O-W-051]. *Journal of Thrombosis & Haemostasis* 2007;5.
89. Friedman RJ, Dunsworth GA. Cost analyses of extended prophylaxis with enoxaparin after hip arthroplasty. *Clin Orthop* 2000;:171-82.
90. Funk L, Cohen A, Woodcock N, et al. Comparison of the efficacy and safety of the A-V impulse system with that of enoxaparin in the prophylaxis of deep venous thrombosis in total knee arthroplasty. *Journal of Bone and Joint Surgery - British Volume* 2000;82:62.
91. Garcia-Zozaya I. Warfarin vs enoxaparin for deep venous thrombosis prophylaxis after total hip & total knee arthroplasty: a cost comparison. *J Ky Med Assoc* 1998;96:143-8.
92. Gillespie W, Murray D, Gregg PJ, et al. Risks and benefits of prophylaxis against venous thromboembolism in orthopaedic surgery. *Journal of Bone and Joint Surgery - Series B* 2000;82:475-9.
93. González Della Valle A, Reynoso FJ, Ben Ari J, et al. The Multimodal Approach for the Prevention of Thromboembolic Disease After Total Joint Arthroplasty. *Semin Arthroplasty* 2009;20:241-50.
94. Gordoís A, Posnett J, Borris L, et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. *J Thromb Haemost* 2003;1:2167-74.
95. Grover VK, Saini D, Bharti N. Deep venous thrombosis: Prophylaxis. *Journal of Anaesthesiology Clinical Pharmacology* 2008;24:3-12.
96. Gurney JW. No fooling around: direct visualization of pulmonary embolism. *Radiology* 1993;188:618-619.
97. Haentjens P. Post-hospital discharge prevention of deep vein thrombosis with nadroparin calcium after elective total hip replacement. The Belgian Nadroparin Post-Hospital Discharge in Orthopedics (NPHDO) Study Group. *Br-J-Anaesth* 1999;82 Suppl 1:78.
98. Haentjens P, De Groote K, Annemans L. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. A cost-utility analysis. *Arch Orthop Trauma Surg* 2004;124:507-17.
99. Haentjens P, on behalf of the Bellgian Nadroparin PostHospital Discharge in Orthopedics Study,Group. Post-hospital discharge prevention of deep vein thrombosis with nadroparin calcium after elective total hip replacement. *Haemostasis* 1998;28:292.

100. Hauch O, Khattar SC, Jorgensen LN. Cost-benefit analysis of prophylaxis against deep vein thrombosis in surgery. *Semin Thromb Hemost* 1991;17:280-3.
101. Hauer W, Sinz G, Niessner H. Hirudin versus enoxaparin as prophylaxis of venous thromboembolism in patients undergoing total hip replacement [abstract]. *Ann Hematol* 1997;74 Suppl 2:A130.
102. Hawkins DW, Langley PC, Krueger KP. A pharmacoeconomic assessment of enoxaparin and warfarin as prophylaxis for deep vein thrombosis in patients undergoing knee replacement surgery. *Clin Ther* 1998;20:182-95.
103. Hawkins DW, Langley PC, Krueger KP. Pharmacoeconomic model of enoxaparin versus heparin for prevention of deep vein thrombosis after total hip replacement. *Am J Health-Syst Pharm* 1997;54:1185-90.
104. Heit J, Berkowitz S, Bona R, et al. Efficacy and safety of normiflo (a LMWH) compared to warfarin for prevention of venous thromboembolism following total knee replacement: a double-blind, dose-ranging study. *Thromb Haemost* 1995;73:978-Abstract.
105. Howard AW, Aaron SD. Low molecular weight heparin is efficacious as DVT prophylaxis following total knee arthroplasty - a meta-analysis of randomized controlled trials [Abstract]. *Journal of Bone and Joint Surgery-British Volume* 1999;81 Suppl 1:104.
106. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother* 1997;31:192-203.
107. Hull RD. New insights into extended prophylaxis after orthopaedic surgery - the North American Fragmin Trial experience. *Haemostasis* 2000;30:95-100.
108. Hull RD, Pineo GF, MacIsaac S. Low-molecular-weight heparin prophylaxis: preoperative versus postoperative initiation in patients undergoing elective hip surgery. *Thromb Res* 2001;101:155-62.
109. Hull RD, Raskob G, Pineo GF, et al. Subcutaneous low-molecular-weight heparin (LMWH) versus warfarin sodium (WS) for prophylaxis of deep-vein thrombosis (DVT) after total hip or total knee replacement (THR/TKR): an economic perspective. *Blood* 1994;84:70a.
110. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin (LMWH) versus warfarin sodium (WS) for prophylaxis of deep-vein thrombosis (DVT) after total hip or total knee replacement (THR/TKR): An economic perspective. *Journal of Vascular Surgery* 1997;Issue:O1579.
111. Jaffe D, Noff M, Peer A, et al. Prophylaxis against deep-vein thrombosis in total knee replacement: comparison of low molecular weight heparin and the A-V Impulse System. *Journal of bone and joint surgery British volume* 1999;81:71.
112. Kaboli PJ. Using elastic compression stockings to prevent post-thrombotic syndrome. *Journal of Respiratory Diseases* 2008;29:100.
113. Kalodiki E, Nicolaides A, AlKutoubi A, et al. Low molecular weight heparin (LMWH) and LMWH plus graduated elastic compression for deep venous thrombosis (DVT) prophylaxis in total hip replacement. *Thromb Haemost* 1993;69:650-Abstract.
114. Kahn SR. Natural history of postthrombotic disease: Transition from acute to chronic disease. *J Vasc Surg* 2010;52:62S-64S.
115. Kalodiki E, Nicolaides AN, AlKutoubi A, et al. LMWH and LMWH plus graduated elastic compression for DVT prophylaxis in total hip replacement. *Thromb Haemost* 1993;69:619-Abstract.
116. Kearon C, Hirsh J. Management of venous thromboembolism. *N Engl J Med* 1997;336:1506-11.
117. Kennon RE, Keggi JM, Wetmore RS, et al. Total hip arthroplasty through a minimally invasive anterior surgical approach. *Journal of Bone and Joint Surgery - Series A* 2003;85:39-48.
118. Kimura S. Perioperative measures of total knee arthroplasty. *Hokkaido Journal of Orthopaedics and Traumatology* 2009;50:185-9.
119. Koss S, Dunn E. Enoxaparin versus adjusted dose heparin in the prevention of deep vein thrombosis after a total hip replacement [Abstract]. *Orthopaedic Transactions* 1996;20:221.
120. Kurth AA, Dahl OE, vanDijk CN, et al. A new oral anticoagulant, dabigatran etexilate, is effective and safe for the prevention of venous thromboembolism after total knee replacement. *The Journal of Bone and Joint Surgery* 2009;91-B:74.
121. Kwong L, Diamantopoulos A, Forster F, et al. Will Rivaroxaban Be Cost-Effective for Prevention of Venous Thromboembolism after Total Hip Replacement in US Patients [Abstract No. 1290]. *Blood* 2008;112:467.
122. Kwong L, Lees M, Sengupta N. Rivaroxaban for Prevention of Venous Thromboembolism after Total Knee Arthroplasty: Impact on Healthcare Costs Based on the RECORD3 Study. *Blood* 2007;110.
123. Kwong L, Sengupta N, Lees M. Rivaroxaban for Prevention of Venous Thromboembolism after Total Knee Replacement: Impact on Healthcare Costs Based on the RECORD4 Study [Abstract No. 1289]. *Blood* 2008;112:466.

124. Kwong LM, Muntz JE. Thromboprophylaxis dosing: the relationship between timing of first administration, efficacy, and safety. *Am J Orthop* 2002;31:16-20.
125. Lassen MR. Comparative efficacy of low-molecular-weight heparins in orthopedic surgery. *Semin Thromb Hemost* 2000;26:53-6.
126. Lassen MR, Turpie AG, Rosencher N, et al. Rivaroxaban: An oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in total knee replacement surgery - Results of the RECORD 3 study.
127. Lassen MR, Turpie AG, Rosencher N, et al. The oral, direct factor Xa inhibitor rivaroxaban vs enoxaparin for prevention of venous thromboembolism after total knee replacement: RECORD3. *Br J Haematol* 2008;141:50-1.
128. Le Balch T, Landais A, Butel J, et al. Enoxaparine (Lovenox(R)), versus standard heparin in prophylaxis of deep vein thrombosis (DVT) after total hip replacement (THR) [Abstract]. *Thromb Haemost* 1987;58:241.
129. Leclerc JR, Geerts WH, Desjardins L. Prevention of venous thromboembolism (VTE) after knee arthroplasty - a randomized, double-blind trial, comparing a low molecular weight heparin fragment (enoxaparin) to warfarin. *Blood* 1994;84:246a-Abstrat.
130. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism (VTE) after knee arthroplasty - A randomized, double-blind trial, comparing a low molecular weight heparin fragment (enoxaparin) to warfarin. *Thromb Haemost* 1995;73:1103-Abstract.
131. Levin LA, Horst M, Bergqvist D. Economic evaluation of desirudin vs heparin in deep vein thrombosis prevention after hip replacement surgery. *Pharmacoeconomics* 1998;13:111-8.
132. Levine MN, Gent M, Hirsh J. Ardeparin plus graduated compression stockings prevented DVT after knee surgery. *Evidence-Based Medicine* 1996;1:213.
133. Lieberman JR, Barnes CL, Lachiewicz PF, et al. Venous thromboembolism debate in joint arthroplasty. *J Bone Joint Surg Am* 2009;91:29-32.
134. Lieberman JR, Huo MM, Hanway J, et al. A comparison of pneumatic compression boots and aspirin versus aspirin alone in prevention of deep venous thrombosis after total hip arthroplasty: A randomized prospective trial [Abstract]. *Orthopaedic Transactions* 1992;16:712-3.
135. Lipp H-. Heparins, heparinoids and hirudin derivatives. Prophylaxis and therapy of venous thromboembolism. *Krankenhauspharmazie* 1999;20:317-32.
136. Livesley E. The A-V impulse system. *Physiotherapy* 1997;83:417-8.
137. Lobo BL. Emerging options for thromboprophylaxis after orthopedic surgery: a review of clinical data. *Pharmacotherapy* 2004;24:66S-72S.
138. Lotke PA. Aspirin prophylaxis for thromboembolic disease after total joint arthroplasty. *Am J Orthop* 2007;36:14-5.
139. Lundkvist J, Bergqvist D, Jonsson B. Cost-effectiveness of extended prophylaxis with fondaparinux compared with low molecular weight heparin against venous thromboembolism in patients undergoing hip fracture surgery. *Eur J Health Econ* 2007;8:313-23.
140. Lyne E, O'Meara PM. Prophylaxis for venous thromboembolism in total hip arthroplasty [1]. *Orthopedics* 1991;14:226,227+230.
141. Mak JCS, Cameron ID, March LM. Evidence-based guidelines for the management of hip fractures in older persons: An update. *Med J Aust* 2010;192:37-41.
142. Marchetti M, Liberato NL, Ruperto N, et al. Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement. *Haematologica* 1999;84:730-7.
143. McCullagh L, Tilson L, Walsh C, et al. A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the Irish healthcare setting. *Pharmacoeconomics* 2009;27:829-46.
144. McLafferty RB. Evidence of prevention and treatment of postthrombotic syndrome. *J Vasc Surg* 2010;52:69S-73S.
145. Menzin J, Colditz GA, Regan MM, et al. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med* 1995;155:757-64.
146. Mol WE, Egberts TC. Prophylaxis for venous thromboembolism in hip fracture surgery: total costs and cost effectiveness in The Netherlands. *Pharmacoeconomics* 1994;5:48-55.
147. More effective, simpler-to-use clot-buster is on the way. Clot-prevention drug could save lives after joint replacement. *Duke Med Health News* 2008;14:6.
148. Morris RJ, Woodcock JP. Evidence-Based Compression: Prevention of Stasis and Deep Vein Thrombosis. *Ann*

Surg 2004;239:162-71.

- 149.Mueck W, Borris LC, Dahl OE, et al. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Haemost* 2008;100:453-61.

- 150.Nerurkar J, Wade WE, Martin BC. Cost/death averted with venous thromboembolism prophylaxis in patients undergoing total knee replacement or knee arthroplasty. *Pharmacotherapy* 2002;22:990-1000.

- 151.Obalum DC, Giwa SO, Adekoya-Cole TO, et al. Deep vein thrombosis: Risk factors and prevention in surgical patients. *West Afr J Med* 2009;28:77-82.

- 152.Olsen J, Gundgaard J, Borris LC. [The cost-effectiveness of fondaparinux compared to enoxaparin as prophylaxis for deep-vein thrombosis in Denmark]. *Ugeskr Laeger* 2005;167:2273-9.

- 153.Ooy A, Hamulyak K. The 'froac trial' - low molecular heparin (LMWH) versus oral anticoagulants (OAC) for prevention of deep venous thrombosis (DVT) in elective hip and knee prosthesis implantations [abstract]. *Acta Orthop Scand* 1995;66:65.

- 154.Palla A, Manganelli D, Rossi G. Prolonged prophylaxis with unfractionated heparin (UH) is effective to reduce delayed deep vein thrombosis (DVT) in total hip replacement (THR). *European Respiratory Journal* 1997;10:5S.

- 155.Pechlaner C, Marschang P. Dabigatran versus enoxaparin after total hip replacement. *Lancet* 2007;370:2002.

- 156.Pellegrini VD, Totterman S, Ayers DC, et al. Comparison of a low molecular weight heparin and warfarin in prevention of deep vein thrombosis after total hip arthroplasty [Abstract]. *Orthopaedic Transactions* 1997;21:520-1.

- 157.Pineo GF, Hull RD, Raskob GE, et al. Subcutaneous low-molecular-weight heparin (LMWH) versus warfarin sodium (WS) for prophylaxis of deep-vein thrombosis (DVT) after total hip or total knee replacement (THR/TKR): An economic perspective. *Sangre* 1995;40:250.

- 158.Planes A, Chastang C, Vochelle N, et al. An equivalence study of two low-molecular-weight heparins (LMWH) in the prevention of deep vein thrombosis (DVT), after total hip replacement (THR) (440 patients). *Thromb Haemost* 1993;69:651-Abstract.

- 159.Planes A, Vochelle N, Fagola J, et al. Efficacy and safety of enoxaparin in prevention of deep venous thrombosis after total hip replacement under spinal anesthesia. Comparison with general anesthesia. *Thromb Haemost* 1989;62:489-Abstract.

- 160.Planes A, Vochelle N, Ferru J, et al. Enoxaparin, low molecular weight heparin: its use in prevention of deep venous thrombosis following total hip replacement. *Thromb Haemost* 1985;54:319-Abstract.

- 161.Preventing blood clots after knee arthroscopy. *Ann Intern Med* 2008;149:40.

- 162.Prevention of venous thrombosis after total hip replacement. *N Engl J Med* 1984;310:927-8.

- 163.Rangarajan S. Inhibitors of coagulation. *Haemophilia* 2011;17:90-94.

- 164.Ranze O, Greinacher A, Hohlfeild RR, et al. Aktuelle Behandlungskonzepte bei Heparin-induzierter Thrombozytopenie. *Dtsch Med Wochenschr* 1999;124:865-73.

- 165.Ruiz Manzano J, Alberich P, Blanquer J, et al. Normativa de profilaxis de la enfermedad tromboembólica venosa. *Arch Bronconeumol* 1996;32:348-56.

- 166.Salvati EA. Thromboembolism after THR: prophylaxis and treatment. *Orthopedics* 1995;18:838-41.

- 167.Samama C-. Épidémiologie de la thrombose veineuse péri-opératoire : Précisions sur les différents niveaux de risque. *Medecine Therapeutique* 1996;2:340-4.

- 168.Sarasin FP, Bounameaux H. Out of hospital antithrombotic prophylaxis after total hip replacement: low-molecular-weight heparin, warfarin, aspirin or nothing? A cost-effectiveness analysis. *Thromb Haemost* 2002;87:586-92.

- 169.Sarasin FP, Bounameaux H. Antithrombotic strategy after total hip replacement. A cost-effectiveness analysis comparing prolonged oral anticoagulants with screening for deep vein thrombosis. *Arch Intern Med* 1996;156:1661-8.

- 170.Schulz SL, Stechemesser B, Seeberger U, et al. Graduated compression stockings for the prevention of venous thromboembolism in surgical patients in the age of low molecular weight heparins [10]. *Journal of Thrombosis and Haemostasis* 2005;3:2363-5.

- 171.Schwartsmann CR, Teloken Drummond SN, Costa RC. Prophylaxis of deep venous thrombosis after total hip replacement: A randomized trial comparing low molecular weight heparin and unfractionated heparin [Poster]. Final programme of 20th World Congress SICOT. Vol.Final programme, pp.486, 1996.

- 172.Scott IA, Lodge RS, Russell DM. Evidence-based guide to perioperative medicine. *Intern Med J* 2007;37:389-401.

- 173.Sculco TP, Colwell Jr. CW, Pellegrini Jr. VD, et al. Prophylaxis against venous thromboembolic disease in patients having a total hip or knee arthroplasty. *Journal of Bone and Joint Surgery - Series A* 2002;84:466-77.
- 174.Sen RK, Kumar A. Venous thrombo-embolism in orthopaedics. *J Indian Med Assoc* 2010;108:215-220.
- 175.Sharrock NE, Brien WW, Salvati EA, et al. The effect of intravenous fixed-dose heparin during total hip arthroplasty on the incidence of deep-vein thrombosis. *Journal of Vascular Surgery* 1992;15:1089.
- 176.Shorr AF, Ramage AS. Enoxaparin for thromboprophylaxis after major trauma: Potential cost implications. *Crit Care Med* 2001;29:1659-65.
- 177.Silbersack Y, Taute BM, Hein W, et al. Prophylactic use of LMWH plus intermittent pneumatic compression prevented DVT in hip or knee arthroplasty. *Evidence-Based Medicine* 2005;10:48.
- 178.Skedgel C, Goeree R, Pleasance S, et al. The cost-effectiveness of extended-duration antithrombotic prophylaxis after total hip arthroplasty. *J Bone Joint Surg Am* 2007;89:819-28.
- 179.Spruill WJ, Wade WE, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in elective hip replacement surgery. *Blood Coagul Fibrinolysis* 2004;15:539-43.
- 180.Spruill WJ, Wade WE, Leslie RB. A cost analysis of fondaparinux versus enoxaparin in total knee arthroplasty. *Am J Ther* 2004;11:3-8.
- 181.Sullivan SD, Kwong L, Nutescu E. Cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against venous thromboembolism in patients undergoing hip fracture surgery. *Value Health* 2006;9:68-76.
- 182.Ten Cate JW. Prevention of deep vein thrombosis following total hip replacement surgery by Orgaran. Summary. *Haemostasis* 1992;22:109-11.
- 183.Thomas DP. Thromboprophylaxis after replacement arthroplasty. *Br Med J* 2001;322:686-7.
- 184.Thomas DP. Whither thromboprophylaxis after total hip replacement? *Journal of Bone and Joint Surgery - Series B* 2000;82:469-72.
- 185.Thomas S, Phillips P, Hughes G. CLOTS: an opportunity missed. *The Lancet* 2009;374:1143.
- 186.Thrombin inhibitor shows stable safety profile in the practice. *MMW Fortschr Med* 2008;150:38-9.
- 187.Tran AH, Lee G. Fondaparinux for prevention of venous thromboembolism in major orthopedic surgery. *Ann Pharmacother* 2003;37:1632-43.
- 188.Tribout B, Colin-Mercier F. New versus established drugs in venous thromboprophylaxis: efficacy and safety considerations related to timing of administration. *Am J Cardiovasc Drugs* 2007;7:1-15.
- 189.Turpie AG. Venous thromboembolism prophylaxis: role of factor xa inhibition by fondaparinux. *Surg Technol Int* 2004;13:261-7.
- 190.Turpie AG. Efficacy of a postoperative regimen of enoxaparin in deep vein thrombosis prophylaxis. *Am J Surg* 1991;161:532-6.
- 191.Turpie AG. Low molecular weight heparins: deep vein thrombosis prophylaxis in elective hip surgery and thrombotic stroke. *Acta Chir Scand Suppl* 1988;543:85-6.
- 192.Turpie AG, Kher A. Prevention of venous thrombosis after elective hip surgery. *Orthopedics* 1998;21:1275-81.
- 193.Urbankova J, Quiroz R, Goldhaber SZ. Intermittent pneumatic compression and deep vein thrombosis prevention in postoperative patients. *Phlebology* 2006;21:19-22.
- 194.Van Ooy A. The "Focal" trial. Low molecular heparin (LMWH) versus oral anticoagulants (OAC) in the prevention of deep venous thrombosis (DVT) in elective hip- and knee prosthesis implants [Abstract]. *Nederlands Tijdschrift voor Orthopaedie* 1995;2:30.
- 195.Verhaeghe R, Verstraete M. Prophylaxis of Venous Thromboembolism in Surgery. *Acta Chir Belg* 1997;106-9.
- 196.Wade WE. Cost analysis of ardeparin versus enoxaparin for the prophylaxis of deep vein thrombosis after knee arthroplasty. *Clin Ther* 1998;20:347-51.
- 197.Wade WE, Hawkins DW. Cost effectiveness of outpatient anticoagulant prophylaxis after total hip arthroplasty. *Orthopedics* 2000;23:335-8.
- 198.Wade WE, Spruill WJ, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in hip fracture surgery. *Am J Ther* 2004;11:194-8.
199. Wade WE, Spruill WJ, Leslie RB. Cost analysis: fondaparinux versus preoperative and postoperative enoxaparin as venous thromboembolic event prophylaxis in elective hip arthroplasty. *Am J Orthop* 2003;32:201-5.
- 200.Warwick D, Bannister G. Does a 3 day peri-operative course of low molecular weight heparin reduce deep venous thrombosis after total hip replacement? *Journal of Bone and Joint Surgery - British Volume* 1995;77-B:173.

201. Warwick D, Harrison J. Pneumatic plantar compression versus low molecular weight heparin in the prevention of deep vein thrombosis after total hip replacement [abstract]. *Journal of Bone and Joint Surgery - British Volume* 1997;79 Suppl 2:259.
 202. Warwick D, Harrison J, Mitchelmore A, et al. Foot pump versus LMWH in the prevention of DVT after THR [abstract]. *Journal of Bone and Joint Surgery - British Volume* 2000;82 Suppl 2:159-60.
 203. Warwick D, Mitchelmore A. Is a short peri-operative course of low molecular weight heparin effective in preventing deep venous thrombosis after total hip replacement? [abstract]. *Journal of Bone and Joint Surgery - British Volume* 1994;76-B Suppl II, III:151.
 204. Warwick D, Samama MM. The contrast between venographic and clinical endpoints in trials of thromboprophylaxis in hip replacement. *Journal of Bone and Joint Surgery - Series B* 2000;82:480-2.
 205. Warwick DJ, Harrison J, Whitehouse SL, et al. Pneumatic plantar compression versus low molecular weight heparin for the prevention of deep vein thrombosis after total knee replacement [abstract]. *Journal of Bone and Joint Surgery - British Volume* 1999;81 Suppl 2:210.
 206. Webb MS, Murphy TP, Dorfman GS. Use and selection of inferior vena cava filters. *Seminars in Respiratory and Critical Care Medicine* 1996;17:71-85.
 207. Weinmann EE, Salzman EW. Trombosis venosa profunda. *Rev Cubana Med* 1996;35:118-35.
 208. Wells P, Diamantopoulos A, Forster F, et al. Cost-Effectiveness of Rivaroxaban as VTE Prophylaxis after Total Hip Replacement in Canada [Abstract No. 1291]. *Blood* 2008;112:467.
 209. Westrich GH, Sculco TP. Pneumatic plantar compression compared with aspirin for deep venous thrombosis prophylaxis after total knee arthroplasty [Abstract]. *Orthopaedic Transactions* 1996;20:398.
 210. Wienert V, Altenkämper H, Berg D, et al. Leitlinien zur apparativen intermittierenden Kompression (AIK). *Phlebologie* 1998;27:96-7.
 211. Wienert V, Altenkämper H, Berg D, et al. Leitlinien zur apparativen intermittierenden Kompression (AIK). *Phlebologie* 1996;25:211-2.
 212. Wilke T, Neumann K, Klapper U, et al. [Oral anticoagulation after major hip or knee replacement surgery: a process-driven managerial pharmacoeconomic analysis in German hospitals]. *Orthopade* 2008;37:448-56.
 213. Wille-Jørgensen P. Prophylaxis of postoperative thromboembolism with a combination of heparin and graduated compression stockings. *International Angiology* 1996;15:15-20.
 214. Wilson JF. In the clinic preoperative evaluation. *Ann Intern Med* 2009;151.
 215. Winslow KA, Hartmannsgruber MWB, Chung JH, et al. Combination of two standard pneumatic calf compression devices to fit the morbidly obese [7]. *Anesthesiology* 2000;93:1159.
 216. Wolowacz SE, Roskell NS, Maciver F, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism after total knee and hip replacement surgery. *Clin Ther* 2009;31:194-212.
 217. Wolowacz SE, Roskell NS, Plumb JM, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism in patients aged over 75 years or with moderate renal impairment undergoing total knee or hip replacement. *Thromb Haemost* 2010;103:360-71.
 218. Working method. *Sang Thrombose Vaisseaux* 2008;20:9-20.
 219. Yeung JMC, Lingam K. Flight related deep vein thrombosis. *Scott Med J* 2002;47:123-6.
 220. Zacharski LR, Ornstein DL. Heparin and cancer. *Thromb Haemost* 1998;80:10-23.
 221. Zonzin P, Agnelli G, Casazza F, et al. Comments on the guidelines of the European Society of Cardiology Task Force on Pulmonary Embolism. *Italian Heart Journal Supplement* 2001;2:1342-56.
- Excluded because the population was not major orthopedic surgery (n=74)
222. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;308:235-46
 223. Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. *Int J Clin Pharmacol Ther* 2001;39:431-46
 224. Camporese G, Bernardi E, Prandoni P, Noventa F, Verlato F, Simioni P, Ntita K, Salmistraro G, Frangos C, Rossi F, Cordova R, Franz F, Zucchetta P, Kontothanassis D, Andreozzi GM. KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group. *Ann Intern Med* 2008;149:73-82
 225. Cohn SM, Moller BA, Feinstein AJ, et al. Prospective trial of low-molecular-weight heparin versus unfractionated heparin in moderately injured patients. *Vasc Surg* 1999;33:219-23
 226. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, Laporte S et al. A clinical trial of vena caval

filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med* 1998; 338:409-416

227. Elliott CG, Dudney TM, Egger M, et al. Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep-vein thrombosis after non-lower extremity trauma. *Journal of Trauma - Injury, Infection and Critical Care* 1999;47:25-32

228. Eppsteiner RW, Shin JJ, Johnson J, et al. Mechanical compression versus subcutaneous heparin therapy in postoperative and posttrauma patients: A systematic review and meta-analysis. *World J Surg* 2010;34:10-9

229. Ettema HB, Kollen BJ, Verheyen CC, Büller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2008;6(7):1093-8

230. Fuchs S, Heyse T, Rudofsky G, et al. Continuous passive motion in the prevention of deep-vein thrombosis. A randomised comparison in trauma patients. *Journal of Bone and Joint Surgery - Series B* 2005;87:1117-22

231. Gajic O, Warner DO, Decker PA, et al. Long-haul air travel before major surgery: A prescription for thromboembolism? *Mayo Clin Proc* 2005;80:728-31

232. Gangireddy C, Rectenwald JR, Upchurch GR, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. *Journal of Vascular Surgery* 2007;45(2):335-341; discussion 341-2

233. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996;335:701-7

234. Ginsberg JS, Brill-Edwards P, Panju A, et al. Pre-operative plasma levels of thrombin-antithrombin III complexes correlate with the development of venous thrombosis after major hip or knee surgery. *Thromb Haemost* 1995;74:602-5

235. Goldhaber SZ, Visani L, De Rosa M, for ICOPER. Acute pulmonary embolism: clinical outcomes in the international cooperative pulmonary embolism registry. *Lancet* 1999;353:1386-1389

236. Greenfield LJ, Proctor MC, Rodriguez JL, et al. Posttrauma thromboembolism prophylaxis. *Journal of Trauma - Injury, Infection and Critical Care* 1997;42:100-3

237. Haentjens P, Blaimont, Blairon, et al. Thromboembolic prophylaxis in orthopaedic trauma patients: A comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium). *Injury* 1996;27:385-90

238. Hakki SI, Fareed J, Hoppensteadt DA, et al. Plasma tissue factor pathway inhibitor levels as a marker for postoperative bleeding after enoxaparin use in deep vein thrombosis prophylaxis in orthopedics and general surgery. *Clin Appl Thromb Hemost* 2001;7:65-71

239. Hakki SI, Fareed J, Hoppensteadt DA, et al. Plasma tissue factor pathway inhibitor levels as a marker for postoperative bleeding after enoxaparin use in deep vein thrombosis prophylaxis in orthopedics and general surgery. *Clin Appl Thromb Hemost* 2000;6:206-12

240. Hansson P-, Eriksson H, Welin L, et al. Smoking and abdominal obesity: Risk factors for venous thromboembolism among middle-aged men: 'The study of men born in 1913'. *Arch Intern Med* 1999;159:1886-90

241. Headrick JR, Barker DE, Pate LM, et al. The role of ultrasonography and inferior vena cava filter placement in high-risk trauma patients. *Am Surg* 1997;63:1-8

242. Hilbert P, Zur Nieden K, Stuttmann R. [D-dimer screening in surgical long-term intensive care patients]. *Anaesthesist* 2005;54:210-4

243. Howard A, Zaccagnini D, Ellis M, et al. Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery. *Br J Surg* 2004;91:842-7

244. Iskander GAP, Nelson RS, Morehouse DL, et al. Incidence and propagation of infrageniculate deep venous thrombosis in trauma patients. *Journal of Trauma - Injury, Infection and Critical Care* 2006;61:695-700

245. Janni W, Bergauer F, Rjosk D, et al. [Prospective randomized study comparing the effectiveness and tolerance of various low-molecular-weight heparins in high risk patients]. *Zentralbl Chir* 2001;126:32-8.

246. Jorgesen PS, Warming T, Hansen K, Paltved C, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venographic controlled study. *Thrombosis Research* 2002;105:477-480

247. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. *Cochrane Database of Systematic Reviews* 2008;Oct 8;(4)

248. Kakkos SK, Caprini JA, Nicolaides AN, et al. Combined modalities in the prevention of venous thromboembolism: A review of the literature. *Phlebology* 2006;21:23-8

249. Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, et al. Review on the value of graduated elastic compression stockings after deep vein thrombosis. *Thromb Haemost* 2006;96:441-5
250. Keller ME, Metzler MH, Phillips JO, et al. Evaluation of a disease management plan for prevention and diagnosis of thromboembolic disease in major trauma patients. *Curr Surg* 2000;57:456-9
251. Knesek MJ, Litinas E, Adiguzel C, et al. Inflammatory biomarker profiling in elderly patients with acute hip fracture treated with heparins. *Clin Appl Thromb Hemost* 2010;16:42-50
252. Knudson MM, Lewis FR, Clinton A, Atkinson K, Megerman J. Prevention of venous thromboembolism in trauma patients. *The Journal of Trauma* 1994;37:480-487
253. Knudson MM, Morabito D, Paiement GD, et al. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *Journal of Trauma - Injury, Infection and Critical Care* 1996;41:446-59
254. Kock H-J, Schmit-Neuburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;346:459-461
255. Kohro S, Yamakage M, Takahashi T, et al. Intermittent pneumatic compression prevents venous stasis in the lower extremities in the lithotomy position. *Canadian Journal of Anesthesia* 2002;49:144-7
256. Kosir MA, Schmittinger L, Barno-Winarski L, et al. Prospective double-arm study of fibrinolysis in surgical patients. *J Surg Res* 1998;74:96-101
257. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. *Haemostasis* 1993;23:20-26
258. Kurtoğlu M, Büyükkurt CD, Dural AC, et al. Venous thromboembolism prophylaxis with low molecular weight heparins in polytraumatized patients in intensive care unit. *Turkish Journal of Surgery* 2001;17:233-42
259. Kussmann J. [Prevention of thromboembolism with low-dose heparin]. *Langenbecks Arch Chir* 1986;369:473-8
260. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, Monreal M, and the RIETE Investigators.
261. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the registro informatizado de la enfermedad tromboembolica venosa (riete) registry. *Circulation*. 2008;117:1711-1716
262. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of deep vein thrombosis after major knee surgery--a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost* 1992;67:417-23
263. Lee AD, Stephen E, Agarwal S, et al. Venous Thrombo-embolism in India. *European Journal of Vascular and Endovascular Surgery* 2009;37:482-5
264. Liem TK, Huynh TM, Moseley SE, et al. Symptomatic perioperative venous thromboembolism is a frequent complication in patients with a history of deep vein thrombosis. *J Vasc Surg* 2010;52:651-657.
265. Lu J-, Knudson MM, Bir N, et al. Fondaparinux for Prevention of Venous Thromboembolism in High-Risk Trauma Patients: A Pilot Study. *J Am Coll Surg* 2009;209:589-94
266. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. *Blood* 2005;106:2710-5
267. McMurtry AL, Owings JT, Anderson JT, et al. Increased use of prophylactic vena cava filters in trauma patients failed to decrease overall incidence of pulmonary embolism. *J Am Coll Surg* 1999;189:314-20
268. Mittlmeier T. The relationship of foot and ankle movements to venous return in the lower limb. *Unfallchirurg* 1999;102:986-7
269. Morris RJ, Woodcock JP. Intermittent pneumatic compression or graduated compression stockings for deep vein thrombosis prophylaxis?: A systematic review of direct clinical comparisons. *Ann Surg* 2010;251:393-6
270. Murakami M, McDill TL, Cindrick-Pounds L, et al. Deep venous thrombosis prophylaxis in trauma: Improved compliance with a novel miniaturized pneumatic compression device. *Journal of Vascular Surgery* 2003;38:923-7
271. Onat L, Ganiyusufoglu AK, Mutlu A, et al. Optease and trapease vena cava filters: A single-center experience in 258 patients. *Cardiovasc Intervent Radiol* 2009;32:992-7
272. Pagella P, Cipolle M, Sacco E, et al. A randomized trial to evaluate compliance in terms of patient comfort and satisfaction of two pneumatic compression devices. *Orthopaedic Nursing* 2007;26:169-74
273. Prandoni P, Lensing AWA, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome. A randomized, controlled trial. *Ann Intern Med* 2004;141:249,256+I
274. Regier DA, Marra CA, Lynd L. Economic evaluations of anticoagulants for the prophylaxis of venous thromboembolism following major trauma. *Expert Review of Pharmacoeconomics and Outcomes Research* 2007;7:403-13
275. Ricotta S, Iorio A, Parise P, et al. Post discharge clinically overt venous thromboembolism in orthopaedic

surgery patients with negative venography - An overview analysis. *Thromb Haemost* 1996;76:887-92

276. Roderick P, Ferris G, Wilson K, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: Systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. *Health Technol Assess* 2005 Dec;9(49):iii-iv, ix-x, 1-78

277. Rogers FB, Shackford SR, Ricci MA, et al. Prophylactic Vena Cava Filter Insertion in Selected High-Risk Orthopaedic Trauma Patients. *J Orthop Trauma* 1997;11:267-72

278. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database of Systematic Reviews* 2010, Issue 7

279. Sajid MS, Tai NRM, Goli G, et al. Knee versus Thigh Length Graduated Compression Stockings for Prevention of Deep Venous Thrombosis: A Systematic Review. *European Journal of Vascular and Endovascular Surgery* 2006;32:730-6

280. Schädlich PK, Kentsch M, Weber M, et al. Cost effectiveness of enoxaparin as prophylaxis against venous thromboembolic complications in acutely ill medical inpatients: Modelling study from the hospital perspective in Germany. *Pharmacoeconomics* 2006;24:571-91

281. Schultz DJ, Brasel KJ, Washington L, et al. Incidence of Asymptomatic Pulmonary Embolism in Moderately to Severely Injured Trauma Patients. *Journal of Trauma - Injury, Infection and Critical Care* 2004;56:727-33

282. Selby R, Geerts W, Ofosu FA, et al. Hypercoagulability after trauma: Hemostatic changes and relationship to venous thromboembolism. *Thromb Res* 2009;124:281-7

283. Sevestre MA, Labarere J, Brin S, et al. Optimizing history taking for evaluating the risk of venous thromboembolism: The OPTIMEV study. *J Mal Vasc* 2006;31:217-27

284. Sharma OP, Oswanski MF, Joseph RJ, et al. Venous thromboembolism in trauma patients. *Am Surg* 2007;73:1173-80

285. Stannard JP, Lopez-Ben RR, Volgas DA, et al. Prophylaxis against deep-vein thrombosis following trauma: A prospective, randomized comparison of mechanical and pharmacologic prophylaxis. *Journal of Bone and Joint Surgery - Series A* 2006;88:261-6

286. Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev*. 2008 Oct 8;(4):CD006681

287. Urayama H, Tanaka K, Fukui D, et al. Increasing Circulation in the Lower Limb under General Anesthesia Using the A-V Impulse System. *Angiology* 2003;54:691-4

288. Urban MK, Jules-Elysee K, MacKenzie CR. Pulmonary embolism after IVC filter. *HSS Journal* 2008;4:74-5

289. Urbankova J, Quiroz R, Goldhaber SZ. Intermittent pneumatic compression and deep vein thrombosis prevention in postoperative patients. *Phlebology* 2006;21:19-22

290. Van Den Berg E, Bathgate B, Panagakos E, et al. Duplex screening as a method of quality assurance of perioperative thromboembolism prophylaxis. *International Angiology* 1999;18:210-9

291. Von Bary S, Krieger S, Sobala KH. Vena-cava filter - Prophylaxis of pulmonary re-embolism. Clinical experience report. *Zentralbl Chir* 1999;124:27-31

292. Wildin CJ, Hui ACW, Esler CNA, et al. In vivo pressure profiles of thigh-length graduated compression stockings. *Br J Surg* 1998;85:1228-31

293. Winslow EH, Brosz DL. Graduated compression stockings in hospitalized postoperative patients: Orrectness of usage and size. *Am J Nurs* 2008;108:40-50

294. Wirth T, Schneider B, Misselwitz F, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. *Arthroscopy* 2001;17:393-9

295. Wu O, Robertson L, Twaddle S, et al. Screening for thrombophilia in high-risk situations: Systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health Technol Assess* 2006;10:1-75

296. Yenna ZC, Roberts C. Thromboprophylaxis after multiple trauma: what treatment and for how long? *Injury* 2009 Nov;40 Suppl 4:S90-4.

Excluded because the study was not controlled (n=70)

297. Altintas F, Gurbuz H, Erdemli B, et al. [Venous thromboembolism prophylaxis in major orthopaedic surgery: A multicenter, prospective, observational study]. *Acta Orthop Traumatol Turc* 2008;42:322-7

298. Altintas F, Gurbuz H, Erdemli B, et al. Venous thromboembolism prophylaxis in major orthopaedic surgery: A multicenter, prospective, observational study. *Acta Orthopaedica et Traumatologica Turcica* 2008;42:322-7

299. Anand S, Asumu T. Patient acceptance of a foot pump device used for thromboprophylaxis. *Acta Orthop Belg* 2007;73:386-9
300. Anderson FA, Jr, Hirsh J, White K, et al. Temporal trends in prevention of venous thromboembolism following primary total hip or knee arthroplasty 1996-2001: findings from the Hip and Knee Registry. *Chest* 2003;124:349S-56S
301. Ball ST, Pinsorsnak P, Amstutz HC, et al. Extended travel after hip arthroplasty surgery. Is it safe?. *J Arthroplasty* 2007;22:29-32
302. Beksac B, Gonzalez Della Valle A, Salvati EA. Thromboembolic disease after total hip arthroplasty: who is at risk? *Clin Orthop* 2006;453:211-24
303. Beksac B, Valle AGD, Salvati EA. Thromboembolic disease after total hip arthroplasty: Who is at risk? *Clin Orthop* 2006;:211-24
304. Berend KR, Lombardi AV, Jr, Mallory TH, et al. Ileus following total hip or knee arthroplasty is associated with increased risk of deep venous thrombosis and pulmonary embolism. *J Arthroplasty* 2004;19:82-6
305. Best AJ, Williams S, Crozier A, et al. Graded compression stockings in elective orthopaedic surgery. An assessment of the in vivo performance of commercially available stockings in patients having hip and knee arthroplasty. *J Bone Joint Surg Br* 2000;82:116-8
306. Caprini JA, Arcelus JJ, Motykie G, et al. The influence of oral anticoagulation therapy on deep vein thrombosis rates four weeks after total hip replacement. *J Vasc Surg* 1999;30:813-20
307. Chelly JE, Schilling D. Thromboprophylaxis and peripheral nerve blocks in patients undergoing joint arthroplasty. *J Arthroplasty* 2008;23:350-4
308. Chotanaphuti T, Ongnamthip P, Silpipat S, et al. The prevalence of thrombophilia and venous thromboembolism in total knee arthroplasty. *Journal of the Medical Association of Thailand* 2007;90:1342-7
309. Cofrancesco E, Cortellaro M, Corradi A, et al. Clinical utility of prothrombin fragment 1+2, thrombin antithrombin III complexes and D-dimer measurements in the diagnosis of deep vein thrombosis following total hip replacement. *Thromb Haemost* 1998;79:509-10
310. Dahl OE, Gudmundsen TE, Bjornara BT, et al. Risk of clinical pulmonary embolism after joint surgery in patients receiving low-molecular-weight heparin prophylaxis in hospital: a 10-year prospective register of 3,954 patients. *Acta Orthop Scand* 2003;74:299-304
311. Dale C, Gallus A, Wycherley A, et al. Prevention of venous thrombosis with minidose warfarin after joint replacement. *BMJ* 1991;303:224
312. de la Caffiniere JY, Mignot M, Bruch JM. [The dangerous blood clot in orthopaedic surgery (author's transl)]. *Rev Chir Orthop Reparatrice Appar Mot* 1981;67:47-58.
313. Della Valle AG, Serota A, Go G, et al. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. *Clin Orthop* 2006;:146-53
314. Ennis RS. Postoperative deep vein thrombosis prophylaxis: a retrospective analysis in 1000 consecutive hip fracture patients treated in a community hospital setting. *J South Orthop Assoc* 2003;12:10-7
315. Finsen V. Duration of thrombosis prophylaxis in orthopaedic surgery. *Ann Chir Gynaecol* 2001;90:105-8
316. Fluh D. [Clinical monitoring and prevention of deep vein thrombosis in an orthopedic department: use of enoxaparin for a year]. *Agressologie* 1990;31:151-3
317. Fujita S, Hirota S, Oda T, Kato Y, Tsukamoto Y, Fuji T. Deep venous thrombosis after total hip or total knee arthroplasty in patients in Japan. *Clin Orthop Relat Res.* 2000 Jun;(375):168-74
318. Gonzalez Della Valle A, Serota A, Go G, et al. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. *Clin Orthop* 2006;444:146-53
319. Hernigou P, Fevrier MJ, Kergrohen F. [Prevention of thromboembolic complications with adapted low-dose of antivitamin K after total hip prosthesis]. *Rev Chir Orthop Reparatrice Appar Mot* 1993;79:577-85
320. Hogdall CK, Hogdall EV, Jorgensen LN, et al. Changes in plasma tetranein following hip surgery with or without thrombotic complications. *Thromb Res* 1992;67:399-405
321. Ishii Y, Matsuda Y, Sakata S, et al. Primary total knee arthroplasty using the Genesis I total knee prosthesis: A 5- to 10-year follow-up study. *Knee* 2005;12:341-5
322. Keeney JA, Clohisy JC, Curry MC, et al. Efficacy of combined modality prophylaxis including short-duration warfarin to prevent venous thromboembolism after total hip arthroplasty. *J Arthroplasty* 2006;21:469-75
323. Kennon R, Keggi J, Zatorski LE, et al. Anterior approach for total hip arthroplasty: Beyond the minimally invasive technique. *Journal of Bone and Joint Surgery - Series A* 2004;86:91-7
324. Khan A, Emberson J, Dowd GS. Standardized mortality ratios and fatal pulmonary embolism rates following total knee replacement: a cohort of 936 consecutive cases. *J Knee Surg* 2002;15:219-22

325. Khatod M, Inacio M, Paxton EW, Bini SA, Namba RS, Burchette RJ, Fithian DC. Knee replacement: epidemiology, outcomes, and trends in Southern California. *Acta Orthop*. 2008 Dec;79(6):812-9
326. Kim Y-H, Yoo J-H, Kim J-S. Factors leading to decreased rates of deep vein thrombosis and pulmonary embolism after total knee arthroplasty. *The Journal of Arthroplasty* 2007;22:974-980
327. Kornberg A, Francis CW, Pellegrini VD, Jr, et al. Comparison of native prothrombin antigen with the prothrombin time for monitoring oral anticoagulant prophylaxis. *Circulation* 1993;88:454-60
328. Lachiewicz PF, Soileau ES. Multimodal prophylaxis for THA with mechanical compression. *Clin Orthop* 2006;453:225-30
329. Leali A, Fetto J, Moroz A. Prevention of thromboembolic disease after non-cemented hip arthroplasty. A multimodal approach. *Acta Orthop Belg* 2002;68:128-34
330. Leclerc JR, Gent M, Hirsh J, et al. The incidence of symptomatic venous thromboembolism after enoxaparin prophylaxis in lower extremity arthroplasty: a cohort study of 1,984 patients. Canadian Collaborative Group. *Chest* 1998;114:115S-8S
331. Lieberman DV, Lieberman D. Proximal deep vein thrombosis after hip fracture surgery in elderly patients despite thromboprophylaxis. *Am J Phys Med Rehabil* 2002;81:745-50.
332. Lombardi AV, Jr, Berend KR, Tucker TL. The incidence and prevention of symptomatic thromboembolic disease following unicompartmental knee arthroplasty. *Orthopedics* 2007;30:46-8.
333. Lotke PA, Lonner JH. The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. *Clin Orthop* 2006;452:175-80
334. Mayer A, Hansen M, Peetz D, et al. [Prevention of thromboembolism in trauma surgery by dose adjustment of low molecular weight heparin depending on levels of TAT and D-dimer]. *Unfallchirurg* 2003;106:1020-8
335. Mayer A, Hansen M, Peetz D, et al. Prevention of thromboembolism in trauma surgery by dose adjustment of low molecular weight heparin depending on levels of TAT and D-dimer. *Unfallchirurg* 2003;106:1020-8
336. Meyer G, Gellert R, Schlömer G, et al. Graduated compression stockings in surgery - Optional or obligatory? *Chirurg* 2004;75:45-57
337. Milbrink J, Bergqvist D. The incidence of symptomatic venous thromboembolic events in orthopaedic surgery when using routine thromboprophylaxis. *Vasa* 2008;37:353-7
338. Montgomery KD, Potter HG, Helfet DL. The detection and management of proximal deep venous thrombosis in patients with acute acetabular fractures: A follow-up report. *J Orthop Trauma* 1997;11:330-6
339. Nathan S, Aleem MA, Thiagarajan P, Das De S. The incidence of proximal deep vein thrombosis following total knee arthroplasty in an Asian population: a Doppler ultrasound study. *J Orthop Surg (Hong Kong)*. 2003 Dec;11(2):184-9
340. Otero-Fernandez R, Gomez-Outes A, Martinez-Gonzalez J, et al. Evaluation of the effectiveness and safety of bemiparin in a large population of orthopedic patients in a normal clinical practice. *Clin Appl Thromb Hemost* 2008;14:75-83
341. Piovella F, Wang CJ, Lu H, Lee K, Lee LH, Lee WC, Turpie AG, Gallus AS, Planès A, Passera R, Rouillon A; AIDA investigators. Deep-vein thrombosis rates after major orthopedic surgery in Asia. An epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. *J Thromb Haemost*. 2005 Dec;3(12):2664-70
342. Pookarnjanamorakot C, Sirisriro R, Eurvilaichit C, Jaovisidha S, Koysombatolan I. The incidence of deep vein thrombosis and pulmonary embolism after total knee arthroplasty: the screening study by radionuclide venography. *J Med Assoc Thai*. 2004 Aug;87(8):869-76
343. Reitman RD, Emerson RH, Higgins LL, et al. A multimodality regimen for deep venous thrombosis prophylaxis in total knee arthroplasty. *J Arthroplasty* 2003;18:161-8
344. Scherff Sorensen T, Jorgensen J. Mechanical prophylaxis against deep vein thrombosis in Charnley hip arthroplasty. *Acta Orthop Scand* 1981;52:69-72.
345. Schellong S, Hesselschwerdt HJ, Paar WD, von Hanstein KL. Rates of proximal deep vein thrombosis as assessed by compression ultrasonography in patients receiving prolonged thromboprophylaxis with low molecular weight heparin after major orthopedic surgery. *Thromb Haemost*. 2005 Sep;94(3):532-6
346. Sharnoff JG, Rosen RL, Palazzo PJ, et al. Prevention of fatal pulmonary thromboembolism by small dose heparin prophylaxis in acute hip fracture surgery. *Br J Clin Pract* 1981;35:390-2
347. Stringer MD, Steadman CA, Hedges AR, et al. Deep vein thrombosis after elective knee surgery. An incidence study in 312 patients. *J Bone Joint Surg Br* 1989;71:492-7
348. Suomalainen O, Kettunen K, Rissanen V, et al. Postoperative thromboembolism and risk factors in elective hip surgery. *Ann Chir Gynaecol* 1983;72:207-13

-
349. Tsuda K, Kawasaki T, Nakamura N, et al. Natural Course of Asymptomatic Deep Venous Thrombosis in Hip Surgery without Pharmacologic Thromboprophylaxis in an Asian Population. *Clin Orthop* 2010;:1-7
-
350. Turpie AG, Lensing AW, Fuji T, et al. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coagul Fibrinolysis* 2009;20:114-21
-
351. Van Heereveld HA, Laan RF, van den Hoogen FH, et al. Prevention of symptomatic thrombosis with short term (low molecular weight) heparin in patients with rheumatoid arthritis after hip or knee replacement. *Ann Rheum Dis* 2001;60:974-6
-
352. Vogel G, Spanuth E. Predictive value of fibrin monomers in postoperative deep vein thrombosis. *Klin Wochenschr* 1990;68:1020-6
-
353. Walsh M, Preston C, Bong M, et al. Relative risk factors for requirement of blood transfusion after total hip arthroplasty. *J Arthroplasty* 2007;22:1162-7
-
354. Wang CJ, wang JW, Chen LM, Chen HS, Yang BY, Cheng SM. Deep Vein Thrombosis after total knee arthroplasty. *J Formos Med Assoc.* 2000;99:848-53
-
355. Wang CJ, Wang JW, Weng LH, Huang CC, Yu PC. Clinical significance of muscular deep-vein thrombosis after total knee arthroplasty. *Chang Gung Med J.* 2007 Jan-Feb;30(1):41-6
-
356. Warwick DJ, Whitehouse S. Symptomatic venous thromboembolism after total knee replacement. *J Bone Joint Surg Br* 1997;79:780-6
-
357. Webb LX, Rush PT, Fuller SB, et al. Greenfield filter prophylaxis of pulmonary embolism in patients undergoing surgery for acetabular fracture. *J Orthop Trauma* 1992;6:139-45
-
358. Westlich GH, Specht LM, Sharrock NE, et al. Venous haemodynamics after total knee arthroplasty. Evaluation of active dorsal to plantar flexion and several mechanical compression devices. *Journal of Bone and Joint Surgery - Series B* 1998;80:1057-66
-
359. Westrich GH, Menezes A, Sharrock N, et al. Thromboembolic disease prophylaxis in total knee arthroplasty using intraoperative heparin and postoperative pneumatic foot compression. *J Arthroplasty* 1999;14:651-6
-
360. Westrich GH, Specht LM, Sharrock NE, et al. Pneumatic compression hemodynamics in total hip arthroplasty. *Clin Orthop* 2000;:180-91.
-
361. White RH, Romano PS, Zhou H, et al. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998;158:1525-31
-
362. Wicky J, Bongard O, Peter R, et al. Screening for proximal deep venous thrombosis using B-mode venous ultrasonography following major hip surgery: implications for clinical management. *Vasa* 1994;23:330-6
-
363. Wilson D, Cooke EA, McNally MA, et al. Altered venous function and deep venous thrombosis following proximal femoral fracture. *Injury* 2002;33:33-9
-
364. Yoo M-, Cho Y-, Ghanem E, et al. Deep vein thrombosis after total hip arthroplasty in Korean patients and D-dimer as a screening tool. *Arch Orthop Trauma Surg* 2009;129:887-94
-
365. Zakarija A, Aledort L. How we treat: Venous thromboembolism prevention in haemophilia patients undergoing major orthopaedic surgery. *Haemophilia* 2009;15(6):1308-10
-
366. Zurawska U, Parasuraman S, Goldhaber SZ. Prevention of pulmonary embolism in general surgery patients. *Circulation* 2007;115
-
- Excluded because the study did not evaluate a comparison of interest (n=138)
-
367. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295-302
-
368. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. RD Heparin Arthroplasty Group. *J Bone Joint Surg Am* 1994;76:1174-85
-
369. Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement. A randomized trial. The German Hip Arthroplasty Trial (GHAT) Group. *Arch Orthop Trauma Surg* 1992;111:110-20
-
370. Low-molecular-weight heparin (enoxaparin) vs dextran 70. The prevention of postoperative deep vein thrombosis after total hip replacement. The Danish Enoxaparin Study Group. *Arch Intern Med* 1991;151:1621-4
-
371. Adolf J, Fritsche HM, Haas S, et al. Comparison of 3,000 IU aXa of the low molecular weight heparin certoparin with 5,000 IU aXa in prevention of deep vein thrombosis after total hip replacement. German Thrombosis Study Group. *Int Angiol* 1999;18:122-6
-
372. Anderson DR, Gross M, Robinson KS, et al. Ultrasonographic screening for deep vein thrombosis following arthroplasty fails to reduce posthospital thromboembolic complications: the Postarthroplasty Screening Study
-

(PASS). *Chest* 1998;114:119S-22S

373. Arcelus JJ, Monreal M, Caprini JA, et al. Clinical presentation and time-course of postoperative venous thromboembolism: Results from the RIETE Registry. *Thromb Haemost* 2008;99:546-51

374. Bae, H.; Westrich, G. H.; Sculco, T. P.; Salvati, E. A.; Reich, L. M. The effect of preoperative donation of autologous blood on deep-vein thrombosis after total hip arthroplasty. *Journal of Bone and Joint Surgery - Vol 83-B, Issue 5*, 676-679

375. Bannasillon V, Dejour H, Besson L, et al. [Prevention of deep venous thrombosis in orthopedic surgery for total hip prosthesis. Randomized trial for determining optimal dosage]. *Ann Chir* 1987;41:377-85

376. Barrellier MT, Lebel B, Parienti JJ, et al. *Thromb Res* 2010;126:e298-304.

377. Barsotti J, Gruel Y, Rosset P, et al. Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a fracture of the neck of the femur. *J Orthop Trauma* 1990;4:371-5

378. Berkowitz SD, Marder VJ, Kosutic G, et al. Oral heparin administration with a novel drug delivery agent (SNAC) in healthy volunteers and patients undergoing elective total hip arthroplasty. *J Thromb Haemost* 2003;1:1914-9

379. Bern MM, Bierbaum B, Wetzner S, et al. Very low dose warfarin as prophylaxis against ultrasound detected deep vein thrombosis following primary hip replacement. *Am J Hematol* 2002;71:69-74

380. Bicalho PS, Hozack WJ, Rothman RH, et al. Treatment of early symptomatic pulmonary embolism after total joint arthroplasty. *J Arthroplasty* 1996;11:522-4

381. Blanchard J, Meuwly JY, Leyvraz PF, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *J Bone Joint Surg Br* 1999;81:654-9

382. Bongard O, Wicky J, Peter R, et al. D-dimer plasma measurement in patients undergoing major hip surgery: use in the prediction and diagnosis of postoperative proximal vein thrombosis. *Thromb Res* 1994;74:487-93

383. Borghi B, Casati A, Rizzoli Study Group on Orthopaedic, Anesthesia. Thromboembolic complications after total hip replacement. *Int Orthop* 2002;26:44-7

384. Borris LC, Breindahl M, Lassen MR, et al. Differences in urinary prothrombin fragment 1 + 2 levels after total hip replacement in relation to venous thromboembolism and bleeding events. *J Thromb Haemost* 2008;6:1671-9

385. Borris LC, Lassen MR, Jensen HP, et al. Perioperative thrombosis prophylaxis with low molecular weight heparins in elective hip surgery. Clinical and economic considerations. *Int J Clin Pharmacol Ther* 1994;32:262-8

386. Borris LC, Sorensen JV, Lassen MR, et al. Components of coagulation and fibrinolysis during thrombosis prophylaxis with a low molecular weight heparin (Enoxaparin) versus Dextran 70 in hip arthroplasty. *Thromb Res* 1991;63:21-8

387. Calfon M, Seddighzadeh A, Piazza G, et al. Deep vein thrombosis in orthopedic surgery. *Clinical and Applied Thrombosis/Hemostasis* 2009;15:512-6

388. Chin CC, Paramsothy M, Aziz YFA. Pulmonary embolism in patients undergoing lower limb orthopaedic surgery. *Asian Oceanian Journal of Radiology* 2003;8:113-5

389. Cohen AT, Skinner JA, Warwick D, et al. The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. *J Bone Joint Surg Br* 2007;89:887-92

390. Colwell CW, Jr, Froimson MI, Mont MA, et al. Thrombosis prevention after total hip arthroplasty: a prospective, randomized trial comparing a mobile compression device with low-molecular-weight heparin. *J Bone Joint Surg Am* 2010;92:527-35

391. Colwell CW, Jr, Kwong LM, Turpie AG, et al. Flexibility in administration of fondaparinux for prevention of symptomatic venous thromboembolism in orthopaedic surgery. *J Arthroplasty* 2006;21:36-45

392. Comerota AJ, Stewart GJ, Alburger PD, et al. Operative venodilation: a previously unsuspected factor in the cause of postoperative deep vein thrombosis. *Surgery* 1989;106:301-8

393. Dulíček P, Pavlata J, Karpas K, et al. Prophylaxis of thromboembolic disease after total hip replacement. *Acta Chir Orthop Traumatol Cech* 2000;67:243-5

394. Eikelboom JW. Effect of fondaparinux 2.5 mg once daily on mortality: A meta-analysis of phase III randomized trials of venous thromboembolism prevention. *European Heart Journal, Supplement* 2008;10

395. Eisele R, Kinzl L, Koelsch T. Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis. *J Bone Joint Surg Am* 2007;89:1050-6

396. Eriksson BI, Borris L, Dahl OE, et al. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2006;4:121-8

397.Eriksson BI, Borris LC, Dahl OE, et al. Dose-escalation study of rivaroxaban (BAY 59-7939)--an oral, direct Factor Xa inhibitor--for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Res* 2007;120:685-93

398.Eriksson BI, Borris LC, Dahl OE, et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation* 2006;114:2374-81

399.Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75

400.Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75

401.Eriksson BI, Dahl OE, Ahnfelt L, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J Thromb Haemost* 2004;2:1573-80

402.Eriksson BI, Kakkar AK, Turpie AG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Joint Surg Br* 2009;91:636-44

403.Eriksson BI, Kalebo P, Ekman S, et al. Direct thrombin inhibition with Rec-hirudin CGP 39393 as prophylaxis of thromboembolic complications after total hip replacement. *Thromb Haemost* 1994;72:227-31

404.Eskander MBF, Limb D, Stone MH, et al. Sequential mechanical and pharmacological thromboprophylaxis in the surgery of hip fractures. *Int Orthop* 1997;21:259-61

405.Faghri PD, Van Meerdervort HF, Glaser RM, et al. Electrical stimulation-induced contraction to reduce blood stasis during arthroplasty. *IEEE Trans Rehabil Eng* 1997;5:62-9

406.Feller JA, Parkin JD, Phillips GW, et al. Prophylaxis against venous thrombosis after total hip arthroplasty. *Aust N Z J Surg* 1992;62:606-10

407.Fender D, Harper WM, Thompson JR, et al. Mortality and fatal pulmonary embolism after primary total hip replacement. Results from a regional hip register. *J Bone Joint Surg Br* 1997;79:896-9

408.Fisher WD, Eriksson BI, Bauer KA, et al. Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. *Thromb Haemost* 2007;97:931-7

409.Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. *J Orthop Trauma*. 1995 Feb;9(1):1-7

410.Francis CW, Marder VJ, Evarts CM. Lower risk of thromboembolic disease after total hip replacement with non-cemented than with cemented prostheses. *Lancet* 1986;1:769-71

411.Francis CW, Pellegrini VD,Jr, Leibert KM, et al. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. *Thromb Haemost* 1996;75:706-11

412.Fredin H, Gustafson C, Rosberg B. Hypotensive anesthesia, thromboprophylaxis and postoperative thromboembolism in total hip arthroplasty. *Acta Anaesthesiol Scand* 1984;28:503-7

413.Fredin HO, Nillius AS. Fatal pulmonary embolism after total hip replacement. *Acta Orthop Scand* 1982;53:407-11

414.Fuji T, Fujita S, Ochi T. Fondaparinux prevents venous thromboembolism after joint replacement surgery in Japanese patients. *Int Orthop* 2008;32:443-51

415.Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement - the influence of preventive intermittent calf compression and of surgical technique. *Br J Surg* 1983;70:17-19

416.Gelfer Y, Tavor H, Oron A, et al. Deep vein thrombosis prevention in joint arthroplasties: continuous enhanced circulation therapy vs low molecular weight heparin. *J Arthroplasty* 2006;21:206-14

417.Giachino AA, Rody K, Turek MA, et al. Systemic fat and thrombus embolization in patients undergoing total knee arthroplasty with regional heparinization. *J Arthroplasty* 2001;16:288-92

418.Ginsberg JS, Nurmohamed MT, Gent M, et al. Use of Hirulog in the prevention of venous thrombosis after major hip or knee surgery. *Circulation* 1994;90:2385-9

419.Haas S. Prevention of deep vein thrombosis in surgical departments. *Unfallchirurg* 2004;107:1065-88

420.Harris WH, Athanasoulis CA, Waltman AC, et al. Prophylaxis of deep-vein thrombosis after total hip replacement. Dextran and external pneumatic compression compared with 1.2 or 0.3 gram of aspirin daily. *J Bone Joint Surg Am* 1985;67:57-62

421.Harris WH, Athanasoulis CA, Waltman AC, et al. High and low-dose aspirin prophylaxis against venous thromboembolic disease in total hip replacement. *J Bone Joint Surg Am* 1982;64:63-6

422.Hartrick CT, Martin G, Kantor G, et al. Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. *Journal of Bone and Joint Surgery - Series A* 2006;88:273-81

- 423.Heit JA, Berkowitz SD, Bona R, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardeparin Arthroplasty Study Group. *Thromb Haemost* 1997;77:32-8
- 424.Heit JA, Elliott CG, Trowbridge AA, et al. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;132:853-61
- 425.Hoek JA, Nurmohamed MT, ten Cate JW, et al. Thrombin-antithrombin III complexes in the prediction of deep vein thrombosis following total hip replacement. *Thromb Haemost* 1989;62:1050-2
- 426.Huang J, Cao Y, Wu L, Gao F. Apixaban versus enoxaparin in patients with total knee arthroplasty: a meta-analysis of randomized trials. *Thromb Haem* 2011;105(2):245-53
- 427.Hui AC, Heras-Palou C, Dunn I, et al. Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement. *J Bone Joint Surg Br* 1996;78:550-4
- 428.Hull RD, Brant RF, Pineo GF, et al. Preoperative vs postoperative initiation of low-molecular-weight heparin prophylaxis against venous thromboembolism in patients undergoing elective hip replacement. *Arch Intern Med* 1999;159:137-41
- 429.Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. *Arch Intern Med* 2001;161:1952-60
- 430.Ishak M, Morely K. Deep venous thrombosis after total hip arthroplasty: a prospective controlled study to determine the prophylactic effect of graded pressure stockings. *Br j Surg* 1981;68:429-432
- 431.Ivanic GM, Moser I, Homann NC, et al. [Intermittent compression devices for swelling reduction and thrombosis prophylaxis--a pilot study after total hip replacement. Is the 2 hour daily minimum application sufficient?]. *Unfallchirurg* 2006;109:786-92
- 432.Ivanic GM, Moser I, Homann NC, et al. Intermittent compression devices for swelling reduction and thrombosis prophylaxis - A pilot study after total hip replacement: Is the 2 hour daily minimum application sufficient? *Unfallchirurg* 2006;109:786-92
- 433.Jeong GK, Gruson KI, Egol KA, et al. Thromboprophylaxis after hip fracture: evaluation of 3 pharmacologic agents. *Am J Orthop* 2007;36:135-40
- 434.Jorgensen PS, Strandberg C, WilleJorgensen P, et al. Early preoperative thromboprophylaxis with Klexane (R) in hip fracture surgery: A placebo-controlled study. *Clinical and Applied Thrombosis/Hemostasis* 1998;4:140-2
- 435.Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9
- 436.Kakkar VV, Howes J, Sharma V, et al. A comparative double-blind, randomised trial of a new second generation LMWH (bemiparin) and UFH in the prevention of post-operative venous thromboembolism. The Bemiparin Assessment group. *Thromb Haemost* 2000;83:523-9
- 437.Kalodiki E, Domjan J, Nicolaides AN, et al. V/Q defects and deep venous thrombosis following total hip replacement. *Clin Radiol* 1995;50:400-3
- 438.Kalodiki E, Nicolaides AN, Al-Kutoubi A, et al. How "gold" is the standard? Interobservers' variation on venograms. *Int Angiol* 1998;17:83-8
- 439.Kew J, Lee YL, Davey IC, Ho SY, Fung KC, Metreweli C. Deep vein thrombosis in elderly Hong Kong Chinese with hip fractures detected with compression ultrasound and Doppler imaging: incidence and effect of low molecular weight heparin. *Arch Orthop Trauma Surg* (1999) 119 :156–158
- 440.Kurt N, Tolunay M, Yüzbaşıoğlu Aslan B. Postoperative venous insufficiency and deep venous thrombosis in total hip replacement: The effects of epidural and general anesthesia. *Artroplasti Artroskopik Cerrahi* 2002;13:215-20
- 441.Labarere J, Bosson J-, Sevestre M-, et al. Thromboprophylaxis with graduated compression stockings for elderly inpatients: More evidence is needed [5]. *Journal of Thrombosis and Haemostasis* 2006;4:1838-40
- 442.Labek G, Bohler N. [Blood transfusion in total hip endoprosthesis operations in relation to Redon drainage and pressure bandages. An innovation in surgical method]. *Z Orthop Ihre Grenzgeb* 1998;136:433-8
- 443.Laguardia AM, Caroli GC. Prevention of deep vein thrombosis in orthopaedic surgery. Comparison of two different treatment protocols with low molecular weight heparin ('Fluxum'). *Curr Med Res Opin* 1992;12:584-93
- 444.Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86

445.Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or Enoxaparin for
446.Thromboprophylaxis after Knee Replacement. *N Engl J Med* 2009;361:594-604.

447.Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, and the ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010; 375: 807–15

448.Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LZ, and the ADVANCE-3 investigators. Randomized Double-Blind Comparison of Apixaban and Enoxaparin for Thromboprophylaxis After Hip Replacement: The ADVANCE-3 Trial. ADVANCE-3 powerpoint presentation

449.Levine MN, Gent M, Hirsh J, et al. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Intern Med* 1996;156:851-6

450.Leyvraz PF, Postel M, Bachmann F, Hoeck JA, Samama M, Vandenbroek D. Prevention of deep vein thrombosis after total hip replacement: randomized comparison between adjusted dose unfractionated heparin and low molecular weight heparin (CY216). In: Hoek JA, ed. Deep vein thrombosis following total hip replacement. PhD thesis, University of Amsterdam, 1990: 105-17.

451.Leyvraz PF, Bachmann F, Hoek J, et al. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *BMJ* 1991;303:543-8

452.Leyvraz PF, Richard J, Bachmann F, et al. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 1983;309:954-8

453.Li T, Lv M, Li Q. [Comprehensive prophylaxis for deep venous thrombosis after proximal femur fractures in geriatric patients]. *Chung Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih* 2008;22:453-5

454.Li XL, Lu WJ, Yu NS. [Prophylaxis for deep vein thrombosis with low molecular weight heparin following hip and knee surgery]. *Chung Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih* 2001;15:39-41

455.Lie SA, Engesaeter LB, Havelin LI, et al. Early postoperative mortality after 67,548 total hip replacements: causes of death and thromboprophylaxis in 68 hospitals in Norway from 1987 to 1999. *Acta Orthop Scand* 2002;73:392-9

456.Messieh M, Huang Z, Johnson LJ, et al. Warfarin responses in total joint and hip fracture patients. *J Arthroplasty* 1999;14:724-9

457.Monreal M, Lafoz E, Roca J, et al. Platelet count, antiplatelet therapy and pulmonary embolism--a prospective study in patients with hip surgery. *Thromb Haemost* 1995;73:380-5

458.Moretti B, Patella V, Pesce V, et al. Combined pharmacological and mechanical prophylaxis for DVT following hip and knee arthroplasty. *Journal of Orthopaedics and Traumatology* 2002;3:149-55

459.Navarro-Quilis A, Castellet E, Rocha E, et al. Efficacy and safety of bemiparin compared with enoxaparin in the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind clinical trial. *J Thromb Haemost* 2003;1:425-32

460.Ndiaye A, Ville D, Clermont N, et al. [Evaluation of the predictive value of fibrin degradation products in the detection of deep venous thrombosis after total knee prosthesis]. *Dakar Med* 1997;42:36-9

461.Norgren L, Austrell C, Brummer R, et al. Low incidence of deep vein thrombosis after total hip replacement: An interim analysis of patients on low molecular weight heparin vs sequential gradient compression prophylaxis. *International Angiology* 1996;15:11-4

462.Norgren L, Toksvig-Larsen S, Magyar G, et al. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. *Int Angiol* 1998;17:93-6

463.O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement. *CMAJ* 1994;150:1083-90

464.Patel VP, Walsh M, Sehgal B, et al. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. *J Bone Joint Surg Am* 2007;89:33-8

465.Pellegrini VD,Jr, Donaldson CT, Farber DC, et al. The Mark Coventry Award: Prevention of readmission for venous thromboembolism after total knee arthroplasty. *Clin Orthop* 2006;452:21-7

466.Pellegrini VD,Jr, Donaldson CT, Farber DC, et al. The John Charnley Award: Prevention of readmission for venous thromboembolic disease after total hip arthroplasty. *Clin Orthop* 2005;441:56-62

467.Pietsch M, Kuhle J, Hamer H, et al. [Mechanical versus drug prevention of thrombosis after total hip endoprosthesis implantation. A randomized, controlled clinical study]. *Biomed Tech (Berl)* 2003;48:207-12

468.Pietsch M, Kuhle J, Hamer H, et al. Mechanical versus pharmacological prophylaxis of deep-vein thrombosis in patients undergoing total hip replacement. A randomized, controlled clinical trial. *Biomed Tech* 2003;48:207-12

469. Pini M, Tagliaferri A, Manotti C, lasagne F, Rinaldi E, Detorri AG. Low molecular weight heparin (Alfa LMWH) compared with unfractionated heparin in prevention of deep-vein thrombosis after hip fractures
470. Pitto RP, Hamer H, Heiss-Dunlop W, et al. Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a randomised clinical trial. *J Bone Joint Surg Br* 2004;86:639-42
471. Pitto RP, Young S. Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: efficacy, safety and patient compliance. A comparative, prospective clinical trial. *Int Orthop* 2008;32:331-6
472. Planes A. Comparison of antithrombotic efficacy and haemorrhagic side-effects of Clivarin versus enoxaparin in patients undergoing total hip replacement surgery. *Blood Coagul Fibrinolysis* 1993;4:S33-5.
473. Planes A, Vochelle N, Fagola M, et al. Comparison of two low-molecular-weight heparins for the prevention of postoperative venous thromboembolism after elective hip surgery. Reviparin Study Group. *Blood Coagul Fibrinolysis* 1998;9:499-505
474. Planes,A.;Vochelle,N.;Ferru,J.;Przyrowski,D.;Clerc,J.;Fagola,M.;Planes,M. Enoxaparine low molecular weight heparin: its use in the prevention of deep venous thrombosis following total hip replacement. *Haemostasis*. 1986;16(2):152-8
475. Poller L, Taberner DA, Sandilands DG, et al. An evaluation of APTT monitoring of low-dose heparin dosage in hip surgery. *Thromb Haemost* 1982;47:50-3
476. Rader CP, Kramer C, Hendrich C, et al. [Experiences with an ankle joint motion device in prevention of thrombosis in patients after total endoprosthesis knee replacement]. *Z Orthop Ihre Grenzgeb* 1998;136:467-70
477. Reber G, Blanchard J, Bounameaux H, et al. Inability of serial fibrin monomer measurements to predict or exclude deep venous thrombosis in asymptomatic patients undergoing total knee arthroplasty. *Blood Coagulation and Fibrinolysis* 2000;11:305-8
478. Rocha E, Alfaro MJ, Paramo JA, et al. Preoperative identification of patients at high risk of deep venous thrombosis despite prophylaxis in total hip replacement. *Thromb Haemost* 1988;59:93-5
479. Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. *Cochrane Database Syst Rev* 2010;4:005981
480. Schuh A, Hausel M, Salminen S. Effect of Tourniquet Use on Blood Loss in Total Knee Arthroplasty. *Zentralbl Chir* 2003;128:866-70
481. Schmidt B, Michler R, Klein M, Faulmann G, Weber C, Schellong S. Ultrasound screening for distal vein thrombosis is not beneficial after major orthopedic surgery. A randomized controlled trial. *Thromb Haemost*. 2003 Nov;90(5):949-54
482. Sharrock NE, Brien WW, Salvati EA, et al. The effect of intravenous fixed-dose heparin during total hip arthroplasty on the incidence of deep-vein thrombosis. A randomized, double-blind trial in patients operated on with epidural anesthesia and controlled hypotension. *J Bone Joint Surg Am* 1990;72:1456-61
483. Sharrock NE, Go G, Mayman D, et al. Decreases in pulmonary artery oxygen saturation during total hip arthroplasty: Variations using 2 leg positioning techniques. *J Arthroplasty* 2005;20:499-502
484. Sharrock NE, Go G, Sculco TP, et al. Dose response of intravenous heparin on markers of thrombosis during primary total hip replacement. *Anesthesiology* 1999;90:981-7
485. Sharrock NE, Go G, Williams-Russo P, et al. Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty. *Br J Anaesth* 1997;79:29-34
486. Spiro TE, Johnson GJ, Christie MJ, et al. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Enoxaparin Clinical Trial Group. *Ann Intern Med* 1994;121:81-9
487. Swierstra BA, Stibbe J, Schouten HJ. Prevention of thrombosis after hip arthroplasty. A prospective study of preoperative oral anticoagulants. *Acta Orthop Scand* 1988;59:139-43
488. Taberner DA, Poller L, Thomson JM, et al. Randomized study of adjusted versus fixed low dose heparin prophylaxis of deep vein thrombosis in hip surgery. *Br J Surg* 1989;76:933-5
489. Tamir L, Hendel D, Neyman C, et al. Sequential foot compression reduces lower limb swelling and pain after total knee arthroplasty. *J Arthroplasty* 1999;14:333-8
490. Turpie AG, Fisher WD, Bauer KA, et al. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost* 2005;3:2479-86
491. Turpie AG, Gallus AS, Hoek JA, et al. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med* 2001;344:619-25
492. Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total

knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-80

493. Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg* 1998;64:1050-8

494. Vives MJ, Hozack WJ, Sharkey PF, et al. Fixed minidose versus-adjusted low-dose warfarin after total joint arthroplasty: A randomized prospective study. *J Arthroplasty* 2001;16:1030-7

495. Vochelle N, Planes A. [Prevention of deep vein thrombosis by enoxaparin after total hip prosthesis]. *Agressologie* 1990;31:145-8

496. Vresilovic EJ, Hozack WJ, Booth RE, Jr, et al. Comparative risk of early postoperative pulmonary embolism after cemented total knee versus total hip arthroplasty with low-dose warfarin prophylaxis. *Am J Knee Surg* 1996;9:2-6

497. Wahlander K, Larson G, Lindahl TL, et al. Factor V Leiden (G1691A) and prothrombin gene G20210A mutations as potential risk factors for venous thromboembolism after total hip or total knee replacement surgery. *Thromb Haemost* 2002;87:580-5

498. Weber U, Koppenhagen K, Malzer H, et al. [Different effectiveness of two preparations of low molecular weight heparin in patients with elective hip joint replacement]. *Langenbecks Arch Chir* 1991;376:147-51

499. Westrich GH, Bottner F, Windsor RE, et al. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. *J Arthroplasty* 2006;21:139-43

500. Westrich GH, Farrell C, Bono JV, et al. The incidence of venous thromboembolism after total hip arthroplasty: a specific hypotensive epidural anesthesia protocol. *J Arthroplasty* 1999;14:456-63

501. Westrich GH, Menezes A, Sharrock N, et al. Thromboembolic disease prophylaxis in total knee arthroplasty using intraoperative heparin and postoperative pneumatic foot compression. *J Arthroplasty* 1999;14:651-6

502. Westrich GH, Salvati EA, Sharrock N, et al. The effect of intraoperative heparin administered during total hip arthroplasty on the incidence of proximal deep vein thrombosis assessed by magnetic resonance venography. *J Arthroplasty* 2005;20:42-50

503. Wilson MG, Pei LF, Malone KM, et al. Fixed low-dose versus adjusted higher-dose warfarin following orthopedic surgery. A randomized prospective trial. *J Arthroplasty* 1994;9:127-30

504. Yoo MC, Kang CS, Kim YH, et al. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *Int Orthop* 1997;21:399-402

Excluded because the study was not a randomized controlled trial or a controlled observational study greater than or equal to 750 participants (n=117)

505. Anders MJ, Lifeso RM, Landis M, et al. Effect of preoperative donation of autologous blood on deep-vein thrombosis following total joint arthroplasty of the hip or knee. *Journal of Bone and Joint Surgery - Series A* 1996;78:574-80.

506. Ares-Rodriguez O, Martinez AH, Fernandez AH, et al. Survival curve and factors related to drainage during the first 24 h after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2008;16:585-9.

507. Arimune M, Morita H. [Safety of low dose unfractionated heparin (LDUH) in patients undergoing hip fracture operation]. *Masui* 2008;57:1223-6.

508. Asensio A, Antolin FJ, Sanchez-Garcia JM, et al. Timing of DVT prophylaxis and risk of postoperative knee prosthesis infection. *Orthopedics* 2010;33:800.

509. Aulmann M, Kwasnicki S, Bottiger BW, et al. Effects of standard unfractionated and low-molecular-weight heparins on platelets of patients undergoing total hip replacement surgery. *Beitr Infusionsther Transfusionsmed* 1997;34:242-7.

510. Bagaria V, Modi N, Panghate A, et al. Incidence and risk factors for development of venous thromboembolism in Indian patients undergoing major orthopaedic surgery: Results of a prospective study. *Postgrad Med J* 2006;82:136-9.

511. Bedair H, Berli M, Gezer S, et al. Hematologic genetic testing in high-risk patients before knee arthroplasty: a pilot study. *Clin Orthop* 2011;469:131-137.

512. Beksac B, Gonzalez Della Valle A, Anderson J, et al. Symptomatic thromboembolism after one-stage bilateral THA with a multimodal prophylaxis protocol. *Clin Orthop* 2007;463:114-9.

513. Beksac B, Valle AGD, Anderson J, et al. Symptomatic thromboembolism after one-stage bilateral THA with a multimodal prophylaxis protocol. *Clin Orthop* 2007;114-9.

514. Bell DF, Harris WH, Kuter DJ, et al. Elevated partial thromboplastin time as an indicator of hemorrhagic risk in postoperative patients on warfarin prophylaxis. *J Arthroplasty* 1988;3:181-4.

515. Bradley JG, Krugener GH, Jager HJ. The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty. *J Arthroplasty* 1993;8:57-61.
516. Britt SL, Barker DE, Maxwell RA, et al. The impact of pelvic and lower extremity fractures on the incidence of lower extremity deep vein thrombosis in high-risk trauma patients. *Am Surg* 2003;69:459-63.
517. Brooks PJ, Keramati M, Wickline A. Thromboembolism in patients undergoing total knee arthroplasty with epidural analgesia. *J Arthroplasty* 2007;22:641-3.
518. Brotman DJ, Jaffer AK, Hurbank JG, et al. Warfarin prophylaxis and venous thromboembolism in the first 5 days following hip and knee arthroplasty. *Thromb Haemost* 2004;92:1012-7.
519. Bruce W, Van der Wall H, Peters M, et al. Occurrence of pulmonary thromboembolism immediately after arthroplasty. *Nucl Med Commun* 2001;22:1237-42.
520. Buchan DS, Bajorek B. Incidence of venous thromboembolism and thromboprophylaxis after total hip or knee arthroplasty. *Journal of Pharmacy Practice and Research* 2008;38:200-4.
521. Buehler KO, D'Lima DD, Petersilge WJ, et al. Late deep venous thrombosis and delayed weightbearing after total hip arthroplasty. *Clin Orthop* 1999;123-30.
522. Chandrasekaran S, Ariaretnam SK, Tsung J, et al. Early mobilization after total knee replacement reduces the incidence of deep venous thrombosis. *ANZ J Surg* 2009;79:526-9.
523. Chotanaphuti T, Jareonarpornwatana A, Laoruengthana A. The mortality rate after thromboembolism prophylaxis in the hip fracture surgery. *J Med Assoc Thai* 2009;92:S115-9.
524. Comfere TB, Sprung J, Case KA, et al. Predictors of mortality following symptomatic pulmonary embolism in patients undergoing noncardiac surgery. *Canadian Journal of Anesthesia* 2007;54:634-41.
525. Dambrosio M, Tullo L, Moretti B, et al. Hemodynamic and respiratory changes during hip and knee arthroplasty: An echocardiographic study. *Minerva Anestesiol* 2002;68:537-47.
526. Daniel J, Pradhan A, Pradhan C, et al. Multimodal thromboprophylaxis following primary hip arthroplasty: the role of adjuvant intermittent pneumatic calf compression. *J Bone Joint Surg Br* 2008;90:562-9.
527. Davidson HC, Mazzu D, Gage BF, et al. Screening for deep venous thrombosis in asymptomatic postoperative orthopedic patients using color Doppler sonography: Analysis of prevalence and risk factors. *Am J Roentgenol* 1996;166:659-62.
528. De Thomasson E, Strauss C, Girard P, et al. Duplex Doppler detection of asymptomatic venous thrombosis after lower limb prosthetic surgery: Retrospective analysis in 400 patients. *Presse Medicale* 2000;29:351-6.
529. Demir M, Iqbal O, Hoppensteadt DA, et al. Anticoagulant and antiprotease profiles of a novel natural heparinomimetic mannopentaose phosphate sulfate (PI-88). *Clinical and Applied Thrombosis/Hemostasis* 2001;7:131-40.
530. Di Panfilo A, Cornette M. [Echo Doppler post total hip arthroplasty: retrospective: study of 111 patients at CHBAH]. *Rev Med Liege* 2004;59:497-503.
531. Eikelboom JW, Mazzarol A, Quinlan DJ, et al. Thromboprophylaxis practice patterns in two Western Australian teaching hospitals. *Haematologica* 2004;89:586-93.
532. Fong YK, Ruban P, Yeo SJ, et al. Use of low molecular weight heparin for prevention of deep vein thrombosis in total knee arthroplasty--a study of its efficacy in an Asian population. *Ann Acad Med Singapore* 2000;29:439-41.
533. Gallay S, Waddell JP, Cardella P, et al. A short course of low-molecular-weight heparin to prevent deep venous thrombosis after elective total hip replacement. *Can J Surg* 1997;40:119-23.
534. Gnudi S, Picci P, Figus E. Thrombo-embolism as a complication of prosthetic replacement operations of the hip: prophylaxis with heparin at low doses. *Ital J Orthop Traumatol* 1980;6:147-51.
535. Gómez Navalón LA, Marín Morales LA, Zorrilla Ribot P, et al. Spinal anesthesia: A protective factor in thromboembolic disease. A retrospective study of 484 arthroplasties. *Rev Esp Anestesiol Reanim* 2001;48:113-6.
536. Grion AM, Gallo U, Bano F, et al. Differences in mortality after hip fracture is associated with postdischarge prescription of antithrombotic prophylaxis: a case control study. *Clin Appl Thrombosis/Hemostasis* 2002;8(2):143-146.
537. Guan Z, Chen Y, Song Y. [Influence of body mass index and age on deep vein thrombosis after total hip and knee arthroplasty]. *Chung Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih* 2006;20:611-5.
538. Guan ZP, Lu HS, Chen YZ, et al. [Clinical risk factors for deep vein thrombosis after total hip and knee arthroplasty]. *Chung Hua Wai Ko Tsa Chih* 2005;43:1317-20.
539. Guyer RD, Booth RE, Jr, Rothman RH. The detection and prevention of pulmonary embolism in total hip replacement. A study comparing aspirin and low-dose warfarin. *J Bone Joint Surg Am* 1982;64:1040-4.

540.Hartman JT, Pugh JL, Smith RD. Cyclic sequential compression of the lower limb in prevention of deep venous thrombosis. *Journal of Bone and Joint Surgery - Series A* 1982;64:1059-62.

541.Heiz-Valle C, de Maistre E, Commun N, et al. [Desirudin (Revasc) to prevent thromboembolic complications after hip or knee replacement surgery]. *Therapie* 2002;57:34-8.

542.Hitos K, Fletcher JP. Venous thromboembolism following primary total knee arthroplasty. *Int Angiol* 2006;25:343-51.

543.Hitos K, Fletcher JP. Venous thromboembolism and fractured neck of femur. *Thromb Haemost* 2005;94:991-6.

544.Hodge WA. Prevention of deep vein thrombosis after total knee arthroplasty. Coumadin versus pneumatic calf compression. *Clin Orthop* 1991;101-5.

545.Hooker JA, Lachiewicz PF, Kelley SS. Efficacy of prophylaxis against thromboembolism with intermittent pneumatic compression after primary and revision total hip arthroplasty. *J Bone Joint Surg Am* 1999;81:690-6.

546.Jaffer AK, Barsoum WK, Krebs V, et al. Duration of anesthesia and venous thromboembolism after hip and knee arthroplasty. *Mayo Clin Proc* 2005;80:732-8.

547.Jain V, Dhal AK, Dhaon BK, et al. Deep vein thrombosis after total hip arthroplasty in Indian patients with and without enoxaparin. *J Orthop Surg* 2004;12:173-7.

548.Jain V, Dahl AK, Dhaon BK, et al. Deep vein thrombosis after total hip arthroplasty in Indian patients. *Postgrad Med J* 2004;80:729-731.

549.Joseph JE, Low J, Courtenay B, et al. A single-centre prospective study of clinical and haemostatic risk factors for venous thromboembolism following lower limb arthroplasty. *Br J Haematol* 2005;129:87-92.

550.Kalodiki E, Domjan J, Nicoladides AN, et al. V/Q defects and deep venous thrombosis following total hip replacement. *Clin Radiology* 1995;50:400-403

551.Keays AC, Mason M, Keays SL, et al. The effect of anticoagulation on the restoration of range of motion after total knee arthroplasty: enoxaparin versus aspirin. *J Arthroplasty* 2003;18:180-5.

552.Kerr J, Linkins LA. High incidence of in-hospital pulmonary embolism following joint arthroplasty with dalteparin prophylaxis. *Thromb Haemost* 2010;103:123-8.

553.Kim GH, Hahn DK, Kellner CP, et al. The incidence of heparin-induced thrombocytopenia Type II in patients with subarachnoid hemorrhage treated with heparin versus enoxaparin: Clinical article. *J Neurosurg* 2009;110:50-7.

554.Kim YH, Kim JS. Factors leading to low prevalence of DVT and pulmonary embolism after THA. Analysis of Genetic and Prothrombotic Factors.

555.Kim YH, Suh JS. Low incidence of deep-vein thrombosis after cementless total hip replacement. *J Bone Joint Surg Am* 1988;70:878-82.*Clin orthop and related research* 2007;465:33-39.

556.Kimura K, Ohtani S, Okamura H, et al. Anticoagulation therapy with heparin and warfarin in total knee arthroplasty for osteoarthritis knee. *Clin Appl Thromb Hemost* 2009;15:109-12.

557.Kovacs MJ, Weir K, MacKinnon K, et al. Body weight does not predict for anti-Xa levels after fixed dose prophylaxis with enoxaparin after orthopedic surgery. *Thromb Res* 1998;91:137-42.

558.Krotenberg R, Adler U, Pomeranz B, et al. Dalteparin vs. enoxaparin as prophylaxis for deep-vein thrombosis after total hip or knee arthroplasty: a retrospective analysis. *Am J Phys Med Rehabil* 2001;80:889-95.

559.Lachiewicz PF, Klein JA, Holleman JB,Jr, et al. Pneumatic compression or aspirin prophylaxis against thromboembolism in total hip arthroplasty. *J South Orthop Assoc* 1996;5:272-80.

560.Laflamme GY, Laflamme GH, Paiement GD, et al. [Efficacy and safety of prophylactic preoperative administration of low-dose warfarin in cemented total knee prostheses]. *Ann Chir* 1994;48:717-22.

561.Larson CM, MacMillan DP, Lachiewicz PF. Thromboembolism after total knee arthroplasty: intermittent pneumatic compression and aspirin prophylaxis. *J South Orthop Assoc* 2001;10:155-63.

562.Lawton RL, Morrey BF. The use of heparin in patients in whom a pulmonary embolism is suspected after total hip arthroplasty. *J Bone Joint Surg Am* 1999;81:1063-72.

563.Lawton RL, Morrey BF, Narr BJ. Validity of index of suspicion for pulmonary embolism after hip arthroplasty. *Clin Orthop* 2003;180-92.

564.Lee BY, Butler G, Al-Waili N, et al. Role of thrombelastograph haemostasis analyser in detection of hypercoagulability following surgery with and without use of intermittent pneumatic compression. *Journal of Medical Engineering and Technology* 2010;34:166-71.

565.Leizorovicz A. Epidemiology of post-operative venous thromboembolism in Asian patients. Results of the SMART venography study. *Haematologica* 2007;92:1194-200.

566.Lin PP, Graham D, Hann LE, et al. Deep venous thrombosis after orthopedic surgery in adult cancer patients. *J*

Surg Oncol 1998;68:41-7.

567.Lindahl TL, Lundahl TH, Nilsson L, et al. APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee--a prospective study. *Thromb Haemost* 1999;81:18-21

568.Lobjoit K. [A retrospective evaluation of venous thrombosis prevention in regulated orthopedic surgery (1986-1989) at the Saint-Germain-en-Laye hospital center]. *Agressologie* 1990;31:158-9.

569.Lowe GDO, Haverkate F, Thompson SG, et al. Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: The ECAT DVT Study. *Thromb Haemost* 1999;81:879-86.

570.Mahlfeld K, Franke J, Schaeper O, et al. [Heparin-induced thrombocytopenia as a complication of postoperative prevention of thromboembolism with unfractionated heparin/low molecular weight heparin after hip and knee prosthesis implantation]. *Unfallchirurg* 2002;105:327-31.

571.Mantilla CB, Horlocker TT, Schroeder DR, et al. Risk factors for clinically relevant pulmonary embolism and deep venous thrombosis in patients undergoing primary hip or knee arthroplasty. *Anesthesiology* 2003;99:552-60.

572.Masri BA, Dunlop DJ, McEwen JA, et al. Can a new design of pneumatic compression device reduce variations in delivered therapy for the mechanical prophylaxis of thromboembolic disease after total hip arthroplasty? *Canadian Journal of Surgery* 2004;47:263-9.

573.McCardel BR, Lachiewicz PF, Jones K. Aspirin prophylaxis and surveillance of pulmonary embolism and deep vein thrombosis in total hip arthroplasty. *J Arthroplasty* 1990;5:181-5.

574.McLaughlin JR, Lee KR. The outcome of total hip replacement in obese and non-obese patients at 10- to 18-years. *Journal of Bone and Joint Surgery - Series B* 2006;88:1286-92.

575.Messieh M. Preoperative risk factors associated with symptomatic pulmonary embolism after total knee arthroplasty. *Orthopedics* 1999;22:1147-9.

576.Mika P, Behounek J, Skotak M, et al. [Complications and risks associated with an anticoagulation therapy combining low molecular weight heparin and Warfarin after total replacement of large joints--our experience]. *Acta Chir Orthop Traumatol Cech* 2004;71:237-44.

577.Mika P, Běhounek J, Skoták M, et al. Complications and risks associated with an anticoagulation therapy combining low molecular weight heparin and warfarin after total replacement of large joints - Our experience. *Acta Chir Orthop Traumatol Cech* 2004;71:237-44.

578.Montrey JS, Kistner RL, Kong AYT. Thromboembolism following hip fracture. *J Trauma* 1985;25:534-7.

579.Nakase J, Toribatake Y, Mouri Y, et al. Heparin versus danaproid for prevention of venous thromboembolism after hip surgery. *J Orthop Surg* 2009;17:6-9.

580.Nathan SS, Simmons KA, Lin PP, et al. Proximal deep vein thrombosis after hip replacement for oncologic indications. *J Bone Joint Surg Am* 2006;88:1066-70.

581.O.buehler K, D'Lima DD, Petersilge WJ, et al. Late deep venous thrombosis and delayed weightbearing after total hip arthroplasty. *Clin Orthop* 1999;123-30.

582.Patel A, Couband D, Feron JM, et al. [Prevention of deep venous thrombosis in arthroplastic surgery of the hip by the combination of heparinotherapy and the antithrombosis stocking]. *Presse medicale* 1988;17(23):1201-3.

583.Pearse EO, Caldwell BF, Lockwood RJ, et al. Early mobilisation after conventional knee replacement may reduce the risk of postoperative venous thromboembolism. *J Bone Joint Surg Br* 2007;89:316-22.

584.Philipp CS, Dilley A, Saidi P, et al. Deletion polymorphism in the angiotensin-converting enzyme gene as a thrombophilic risk factor after hip arthroplasty. *Thromb Haemost* 1998;80:869-73.

585.Piecuch W, Sokolowska B, Dmoszynska A, et al. [Evaluation of selected parameters of blood coagulation and fibrinolysis system in patients undergoing total hip replacement surgery with normovolemic hemodilution procedure and standard enoxaparine prophylaxis]. *Chir Narzadow Ruchu Ortop Pol* 2003;68:95-9.

586.Qiu XS, Wang F, Yao C, et al. Association Between Deep Vein Thrombosis and the Temperature at the Popliteal Fossa During Cement Curing in Total Knee Arthroplasty. *J Arthroplasty* 2011;26:414-418.

587.Rader CP, Kramer C, Konig A, et al. Comparison of low molecular weight and PTT adjusted heparin for thromboprophylaxis in patients with total hip and total knee arthroplasty. *Z Orthop Ihre* 1997;135:52-7.

588.Radziejewicz P, Gregosiewicz A, Bednarek A, et al. [The attempt of identification of the essentials risk factors of venous thromboembolism after hip arthroplasty despite of pharmacological prophylaxis]. *Chir Narzadow Ruchu Ortop Pol* 2010;75:242-247.

589.Saltiel E, Shane R. Evaluating costs of a pharmacist-run thromboprophylaxis program. *Formulary* 1996;31:276-90.

590.Salvati EA, Della Valle AG, Westrich GH, et al. The John Charnley award: Heritable thrombophilia and

development of thromboembolic disease after total hip arthroplasty. *Clin Orthop* 2005;40:55.

591. Sanchez-Ballester J, Smith M, Hassan K, et al. Wound infection in the management of hip fractures: a comparison between low-molecular weight heparin and mechanical prophylaxis. *Acta Orthop Belg* 2005;71:55-9.

592. Sasaki S, Miyakoshi N, Matsuura H, et al. Prospective randomized controlled trial on the effect of fondaparinux sodium for prevention of venous thromboembolism after hip fracture surgery. *J Orthop Sci* 2009;14:491-6.

593. Saunders ME, Grant RE. Cost effectiveness of low-molecular weight heparin versus warfarin following hip replacement surgery. *J Natl Med Assoc* 1998;90:677-80.

594. Schiff RL, Kahn SR, Shrier I, et al. Identifying orthopedic patients at high risk for venous thromboembolism despite thromboprophylaxis. *Chest* 2005;128:3364-71.

595. Seyfert C, Schulz K, Pap G. The influence of the drain suction in knee arthroplasty. *Zentralbl Chir* 2002;127:886-9

596. Shaieb MD, Watson BN, Atkinson RE. Bleeding complications with enoxaparin for deep venous thrombosis prophylaxis. *J Arthroplasty* 1999;14:432-8.

597. Sharrock NE, Hargett MJ, Urquhart B, et al. Factors affecting deep vein thrombosis rate following total knee arthroplasty under epidural anesthesia. *J Arthroplasty* 1993;8:133-9.

598. Sokolowska B, Piecuch W, Walter-Croneck A, et al. [Evaluation of selected parameters of blood coagulation and the fibrinolysis system in patients undergoing total hip replacement]. *Przegl Lek* 2002;59:502-8.

599. Solis MM, Ranval TJ, Nix ML, et al. Is anticoagulation indicated for asymptomatic postoperative calf vein thrombosis?. *J Vasc Surg* 1992;16:414-8.

600. Stern SH, Wixson RL, O'Connor D. Evaluation of the safety and efficacy of enoxaparin and warfarin for prevention of deep vein thrombosis after total knee arthroplasty. *J Arthroplasty* 2000;15:153-8.

601. Stulberg BN, Insall JN, Williams GW, et al. Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg Am* 1984;66:194-201.

602. Svensson PJ, Benoni G, Fredin H, et al. Female gender and resistance to activated protein C (FV:Q506) as potential risk factors for thrombosis after elective hip arthroplasty. *Thromb Haemost* 1997;78:993-6.

603. Szucs G, Ajzner E, Muszbek L, et al. Assessment of thrombotic risk factors predisposing to thromboembolic complications in prosthetic orthopedic surgery. *J Orthop Sci* 2009;14:484-90.

604. Tian H, Song F, Zhang K, et al. [Efficacy and safety of aspirin in prevention of venous thromboembolism after total joint arthroplasty]. *Chung Hua I Hsueh Tsa Chih* 2007;87:3349-52.

605. Torigoshi T, Motokawa S, Maeda Y, et al. Clinical relevance of heparin-PF4 complex antibody in DVT after total joint replacement. *BMC Musculoskelet Disord* 2009;10:42.

606. Trowbridge A, Boese CK, Woodruff B, et al. Incidence of posthospitalization proximal deep venous thrombosis after total hip arthroplasty. *Clin Orthop and related research* 1993;299:203-208.

607. Tsiridis E, Gamie Z, George MJ, et al. Early postoperative bleeding in polytrauma patients treated with fondaparinux: literature review and institutional experience. *Curr Vasc Pharmacol* 2011;9:42-47.

608. Urbach D, Matzen KA, Heitmann D, et al. Relation between peri-operative antithrombin activity and deep vein thrombosis after elective hip replacement surgery. *Vasa* 2003;32:14-7.

609. Villemur B, Bosson JL, Diamand JM. [Deep venous thrombosis (DVT) after hip or knee prosthesis. Evaluation of practices for prevention and prevalence of DVT on doppler ultrasonography]. *J Mal Vasc* 1998;23:257-62.

610. Wang CJ, Wang JW, Weng LH, et al. Prevention of deep-vein thrombosis after total knee arthroplasty in Asian patients. Comparison of low-molecular-weight heparin and indomethacin. *J Bone Joint Surg Am* 2004;86-A:136-40.

611. Westrich GH, Weksler BB, Glueck CJ, et al. Correlation of thrombophilia and hypofibrinolysis with pulmonary embolism following total hip arthroplasty: An analysis of genetic factors. *Journal of Bone and Joint Surgery - Series A* 2002;84:2161-7.

612. Wille-Jorgensen P, Christensen SW, Bjerg-Nielsen A, et al. Prevention of thromboembolism following elective hip surgery. The value of regional anesthesia and graded compression stockings. *Clin Orthop* 1989;:163-7.

613. Wolf LR, Hozack WJ, Balderston RA, et al. Pulmonary embolism. Incidence in primary cemented and uncemented total hip arthroplasty using low-dose sodium warfarin prophylaxis. *J Arthroplasty* 1992;7:465-70.

614. Woolson ST. Intermittent pneumatic compression prophylaxis for proximal deep venous thrombosis after total hip replacement. *J Bone Joint Surg Am* 1996;78:1735-40.

615. Woolson ST. The resolution of deep venous thrombosis that occurs after total joint arthroplasty. A study of thrombi treated with anticoagulation and observed by repeat venous ultrasound scans. *Clin Orthop* 1994;:86-91.

616. Woolson ST, Zehnder JL, Maloney WJ. Factor V Leiden and the risk of proximal venous thrombosis after total hip arthroplasty. *J Arthroplasty* 1998;13:207-10.

617. Yang G, Lu H, Gao J, et al. [Low-molecular-weight heparin for preventing deep-vein thrombosis after total joint arthroplasty]. *Chung Hua Wai Ko Tsa Chih* 2000;38:25-7.

618. Yang Y-, Wang J-, Wu Y-, et al. Effects of different operation on postoperative deep venous thrombosis in lower extremities of old patients with femoral neck fracture. *Journal of Jilin University Medicine Edition* 2008;34:150-2.

619. Yang Z, Liu X, Dai S, et al. [Effectiveness of low molecular weight heparin for prevention of deep vein thrombosis after total hip arthroplasty]. *Chung-Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih/Chinese Journal of Reparative & Reconstructive Surgery* 2010;24:1058-1061.

620. Yoon H-, Han C-, Yang I-. Comparison of Simultaneous Bilateral and Staged Bilateral Total Knee Arthroplasty in Terms of Perioperative Complications. *J Arthroplasty* 2010;25:179-85.

621. Zhao JZ; Song ZZ, Jian H, et al. Venous thromboembolism following total hip replacement and acute physiology and chronic health evaluation scores: A retrospective analysis of 98 cases. *J Clin Rehab Tissue Eng Res* 2010;14:4050-4052.

622. Zhou W, Liu DH, Ma GT, et al. Relationship between pneumatic tourniquet application in total knee arthroplasty and hypercoagulability. *J Clin Rehab Tissue Eng Res* 2011;15:1541-1544.

Excluded because the study did no report an outcome of interest (n=20)

623. Aglietti P, Baldini A, Vena LM, et al. Effect of tourniquet use on activation of coagulation in total knee replacement. *Clin Orthop* 2000;169-77.

624. Bell GK, Goldhaber SZ. Cost implications of low molecular weight heparins as prophylaxis following total hip and knee replacement. *Vasc Med* 2001;6:23-9.

625. Benkő T, Cooke EA, McNally MA, et al. Graduated compression stockings: Knee length or thigh length. *Clin Orthop* 2001;197-203.

626. Cooke EA, Benkő T, O'Connell BM, et al. The effect of graduated compression stockings on lower limb venous haemodynamics. *Phlebology* 1996;11:141-5.

627. Dranitsaris G, Kahn SR, Stumpo C, et al. Pharmacoeconomic analysis of fondaparinux versus enoxaparin for the prevention of thromboembolic events in orthopedic surgery patients. *Am J Cardiovasc Drugs* 2004;4:325-33.

628. Fujisawa M, Naito M, Asayama I, et al. Effect of calf-thigh intermittent pneumatic compression device after total hip arthroplasty: comparative analysis with plantar compression on the effectiveness of reducing thrombogenesis and leg swelling. *J Orthop Sci* 2003;8:807-11.

629. Honorato J, Gomez-Outes A, Navarro-Quilis A, et al. Pharmacoeconomic analysis of bemiparin and enoxaparin as prophylaxis for venous thromboembolism in total knee replacement surgery. *Pharmacoeconomics* 2004;22:885-94.

630. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation. An economic perspective. *Arch Intern Med* 1997;157:298-303.

631. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation: An economic perspective. *Arch Intern Med* 1997;157:298-303.

632. Ilfeld BM, Le LT, Meyer RS, et al. Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartiment total knee arthroplasty: A randomized, triple-masked, placebo-controlled study. *Anesthesiology* 2008;108:703-13.

633. Ishii Y, Matsuda Y. Effect of the timing of tourniquet release on perioperative blood loss associated with cementless total knee arthroplasty: A prospective randomized study. *J Arthroplasty* 2005;20:977-83.

634. Levin LA, Bergqvist D. Cost effectiveness of desirudin compared with a low molecular weight heparin in the prevention of deep vein thrombosis after total hip replacement surgery. *Pharmacoeconomics* 2001;19:589-97.

635. Macaulay W, Westrich G, Sharrock N, et al. Effect of pneumatic compression on fibrinolysis after total hip arthroplasty. *Clin Orthop* 2002;168-76.

636. Markel DC, Urquhart B, Derkowska I, et al. Effect of epidural analgesia on venous blood flow after hip arthroplasty. *Clin Orthop* 1997;168-74.

637. Neal BC, Rodgers A, Gray H, et al. No effect of low-dose aspirin for the prevention of heterotopic bone formation after total hip replacement: a randomized trial of 2,649 patients. *Acta Orthop Scand* 2000;71:129-34.

638.	Ofosu FA, Leclerc J, Delorme F, et al. The low molecular weight heparin Enoxaparin inhibits the consumption of factor VII and prothrombin activation in vivo associated with elective knee replacement surgery. <i>Br J Haematol</i> 1992;82:391-9.
639.	Ofosu FA, Levine M, Craven S, et al. Prophylactically equivalent doses of Enoxaparin and unfractionated heparin inhibit in vivo coagulation to the same extent. <i>Br J Haematol</i> 1992;82:400-5.
640.	Sorensen JV, Lassen MR, Borris LC, et al. Reduction of plasma levels of prothrombin fragments 1 and 2 during thromboprophylaxis with a low-molecular-weight heparin. <i>Blood Coagul Fibrinolysis</i> 1992;3:55-9.
641.	Tetro AM, Rudan JF. The effects of a pneumatic tourniquet on blood loss in total knee arthroplasty. <i>Canadian Journal of Surgery</i> 2001;44:33-8.
642.	Williams LA, Owen TD. Above-knee versus below-knee stockings in total knee arthroplasty. <i>Ann R Coll Surg Engl</i> 2006;88:302-5.
Excluded because the reported outcomes of interest did not meet diagnostic inclusion criteria (n=15)	
643.	Anders JO, Fuhrmann R, Roth A, et al. [Can the number of thromboembolisms incidents in total hips replacement be further reduced?]. <i>Z Orthop Ihre Grenzgeb</i> 2004;142:328-32.
644.	Asano H, Matsubara M, Suzuki K, et al. Prevention of pulmonary embolism by a foot sole pump. <i>Journal of Bone and Joint Surgery - Series B</i> 2001;83:1130-2.
645.	Comp P, Happe LE, Sarnes M, et al. Venous thromboembolism clinically detected after hip fracture surgery with prophylaxis in a clinical practice setting. <i>Am J Orthop</i> 2008;37:470-5.
646.	Figus E, Gnudi S, Cagnano R. Thromboembolism in total hip replacement. <i>Ital J Orthop Traumatol</i> 1983;9:67-70.
647.	Fordyce MJ, Baker AS, Staddon GE. Efficacy of fixed minidose warfarin prophylaxis in total hip replacement. <i>BMJ</i> 1991;303:219-20.
648.	Kaempffe FA, Lifeso RM, Meinking C. Intermittent pneumatic compression versus coumadin. Prevention of deep vein thrombosis in lower-extremity total joint arthroplasty. <i>Clin Orthop</i> 1991;:89-97.
649.	Maezawa K, Nozawa M, Aritomi K, et al. Changes of D-dimer after total hip arthroplasty in patients with and without intraoperative heparin. <i>Arch Orthop Trauma Surg</i> 2008;128:37-40.
650.	Mohr DN, Silverstein MD, Ilstrup DM, et al. Venous thromboembolism associated with hip and knee arthroplasty: current prophylactic practices and outcomes. <i>Mayo Clin Proc</i> 1992;67:861-70.
651.	Muntz JE, O'Connor PJ, Yin H, et al. Factors associated with thromboprophylaxis for orthopedic patients and their impact on outcome. <i>Am J Orthop</i> 2007;36:193-7.
652.	Ohlund C, Fransson SG, Starck SA. Calf compressin for prevention of thromboembolism following hip surgery. <i>Acta Orthop Scand</i> 1983;54:896-899.
653.	Paramo JA, Alfaro MJ, Rocha E. Postoperative changes in the plasmatic levels of tissue-type plasminogen activator and its fast-acting inhibitor--relationship to deep vein thrombosis and influence of prophylaxis. <i>Thromb Haemost</i> 1985;54:713-6.
654.	Proctor MC, Greenfield LJ, Wakefield TW, et al. A clinical comparison of pneumatic compression devices: The basis for selection. <i>Journal of Vascular Surgery</i> 2001;34:459-64.
655.	Sweetland S, Green J, Liu B, et al. Duration and magnitude of the postoperative venous thromboembolism in middle aged women:prospective cohort study. <i>BMJ</i> 2009;339:b4583
656.	Tomita M, Motokawa S. Intraoperative heparin injection reduced D-dimer and TAT levels after total hip arthroplasty. <i>Acta Med Nagasaki</i> 2008;53:9-13.
657.	White RH, Gettner S, Newman JM, et al. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. <i>N Engl J Med</i> 2000;343:1758-64.

Table 2. Excluded studies at the full text level from search two

Excluded as a duplicate publication (n=1)

658.	Camporese G, Bernardi E, Prandoni P, et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. <i>Ann Intern Med</i> 2008;149:73-82.
Excluded because citation was not a full text systematic review, study or trial (n=25)	
659.	Heparin prophylaxis for a leg cast?. <i>Prescrire Int</i> 2003;12:159.
660.	Archibeck MJ, White Jr. RE. What's new in adult reconstructive knee surgery. <i>Journal of Bone and Joint Surgery – Series A</i> 2003;85:1404-11.

661. Balleisen L. [Prevention of embolisms]. *Internist (Berl)* 1998;39:1078-9.

662. Camporese G, Bernardi E, Prandoni P, et al. Graduated compression stockings versus low molecular-weight heparin for prevention of deep vein thrombosis after knee arthroscopy. A randomized trial. *Pathophysiology of Haemostasis and Thrombosis* 2008;36:A21.

663. Cole PA. What's New in Orthopaedic Trauma. *Journal of Bone and Joint Surgery – Series A* 2003;85:2260-9.

664. Cole PA, Bhandari M. What's new in orthopaedic trauma. *Journal of Bone and Joint Surgery – Series A* 2006;88:2545-61.

665. Cole PA, Bhandari M. What's new in orthopaedic trauma. *Journal of Bone and Joint Surgery – Series A* 2005;87:2823-38.

666. Cole PA, Bhandari M. Specialty update: What's new in orthopaedic trauma. *Journal of Bone and Joint Surgery – Series A* 2004;86:2782-95.

667. Gadgil A, Thomas RH. Current trends in thromboprophylaxis in surgery of the foot and ankle. *Foot Ankle Int* 2007;28:1069-73.

668. Graftieaux JP. Neurosurgical air embolisms. Transesophageal echocardiography and dogmatic positions. *Ann Fr Anesth Reanim* 2001;20:587-91.

669. Gupta A, Lutz GE. Synovial cysts: To fuse or not to fuse? *Spine J* 2010;10:817-819.

670. Habscheid W, Spannagel U, Kujath P, et al. [Prevention of thrombosis with low molecular weight heparin in ambulatory patients with injury of the lower extremity: an ultrasound study]. *Vasa Suppl* 1991;33:222-3.

671. Habscheid W, Spannagel U, Kujath P, et al. Thrombosis prophylaxis with low molecular heparin in ambulatory patients with injuries of the lower limb: A sonographic study. *THROMBOSEPROPHYLAXE MIT NIEDERMOLEKULAREM HEPARIN BEI AMBULANTEN PATIENTEN MIT VERLETZUNG DER UNTEREN EXTREMITAT: EINE SONOGRAPHISCHE STUDIE. VASA J.VASC.DIS* 1991;20:222-3.

672. Jorgensen LN, Lykke J. [Thrombosis prophylaxis in knee arthroscopy. A survey of a Cochrane review]. *Ugeskr Laeger* 2008;170:3646-9.

673. Kooli M, Houissa M, Zlitni M. Thromboembolic diseases in the orthopedic setting. *Tunisie Medicale* 2005;83:17-23.

674. Kotani N, Tanioka F, Tsubo T, et al. Systemic heparinization during postoperative pulmonary embolism induces fatal complications [3]. *Eur J Anaesthesiol* 2002;19:382-4.

675. Leyes M, Torres R, Guillén P. Complications of open reduction and internal fixation of ankle fractures. *Foot Ankle Clin* 2003;8:131-47.

676. Ozier Y, Lentschener C. Non-pharmacological approaches to decrease surgical blood loss. *Canadian Journal of Anesthesia* 2003;50.

677. Ploumis A, Ponnappan RK, Bessey JT, et al. Thromboprophylaxis in spinal trauma surgery: consensus among spine trauma surgeons. *Spine Journal* 2009;9:530-6.

678. Sabharwal S. Blount disease. *J Bone Jt Surg Ser A* 2009;91:1758-76.

679. Scalea TM. Optimal timing of fracture fixation: Have we learned anything in the past 20 years? *J Trauma Inj Infect Crit Care* 2008;65:253-60.

680. Weinlein J, Schmidt AH. What's new in orthopaedic trauma? *J Bone Jt Surg Ser A* 2010;92:2247-2260.

681. Wirth T, Misselwitz F, Schneider B, et al. Low molecular weight heparin (reviparin) for the prevention of venous thromboembolism after knee arthroscopy. Results of a randomized controlled trial. *Ann Hematol* 2001;80:A72.

682. Wolf N, Meiser H, Berg U, et al. [Ambulatory prevention of thrombosis in a traumatologic patient sample]. *Vasa Suppl* 1992;35:109.

683. Yuan PS, Albert TJ. Nonsurgical and surgical management of lumbar spinal stenosis. *Journal of Bone and Joint Surgery - Series A* 2004;86:2320-30.

Excluded because the study was not conducted in humans (n=1)

684. Duhautois B. L'enclouage verrouillé dans le traitement des fractures du chien et du chat: Étude rétrospective sur 121 cas (1992-1999). *Pratique Medicale et Chirurgicale de l'Animal de Compagnie* 2001;36:481-96.

Excluded because the population was outside of orthopedic surgeries of interest (n=24)

685. Aito S, Pieri A, D'Andrea M, et al. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. *Spinal Cord* 2002;40:300-3.

686. Baba-Ahmed M, Le Gal G, Couturaud F, et al. High frequency of factor V Leiden in surgical patients with symptomatic venous thromboembolism despite prophylaxis. *Thromb Haemost* 2007;97:171-5.

687. Catre MG. Anticoagulation in spinal surgery. A critical review of the literature. *Canadian Journal of Surgery* 1997;40:413-7.
 688. Cheng JS, Arnold PM, Anderson PA, et al. Anticoagulation risk in spine surgery. *Spine* 2010;35
 689. Chylarecki C, Hierholzer G, Rudofsky G. [Physical prevention of thrombosis with the ankle joint with the motorized ankle joint movement device. Initial results of a clinical study]. *Unfallchirurgie* 1995;21:137-47.
 690. Collen JF, Jackson JL, Shorr AF, et al. Prevention of venous thromboembolism in neurosurgery: A metaanalysis. *Chest* 2008;134:237-49.
 691. Gallus AS, Hirsh J, O'Brien SE, et al. Prevention of venous thrombosis with small, subcutaneous doses of heparin. *JAMA* 1976;235:1980-2.
 692. Glotzbecker MP, Bono CM, Wood KB, et al. Thromboembolic disease in spinal surgery: A systematic review. *Spine* 2009;34:291-303.
 693. Jameson SS, Bottle A, Malviya A, et al. The impact of national guidelines for the prophylaxis of venous thromboembolism on the complications of arthroplasty of the lower limb. *J Bone Joint Surg Br* 2010;92:123-9.
 694. Jorgensen PS, Warming T, Hansen K, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venographic controlled study. *Thromb Res* 2002;105:477-80.
 695. Kim HJ, Walcott-Sapp S, Adler RS, et al. Thromboembolic Complications Following Spine Surgery Assessed with Spiral CT Scans. *HSS J* 2011;7:37-40.
 696. Li T, Lv M, Li Q. [Comprehensive prophylaxis for deep venous thrombosis after proximal femur fractures in geriatric patients]. *Chung Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih* 2008;22:453-5.
 697. Maffulli N, Waterston SW, Squair J, et al. Changing incidence of achilles tendon rupture in Scotland: A 15-year study. *Clin J Sport Med* 1999; 9:157-60.
 698. Mora S, Zalavras CG, Wang L, et al. The role of pulsatile cold compression in edema resolution following ankle fractures: A randomized clinical trial. *Foot and Ankle International* 2002;23:999-1002.
 699. Ploumis A, Ponnappan RK, Maltenfort MG, et al. Thromboprophylaxis in patients with acute spinal injuries: An evidence-based analysis. *Journal of Bone and Joint Surgery - Series A* 2009;91:2568-76.
 700. Sansone JM, Del Rio AM, Anderson PA. The prevalence of and specific risk factors for venous thromboembolic disease following elective spine surgery. *J Bone Jt Surg Ser A* 2010;92:304-313.
 701. Schellong SM, Beyer J, Kakkar AK, et al. Ultrasound screening for asymptomatic deep vein thrombosis after major orthopaedic surgery: the VENUS study. *J Thromb Haemost* 2007; 5:1431-7.
 702. Smith WD, Dakwar E, Le TV, Christian G, et al. Minimally invasive surgery for traumatic spinal pathologies: A mini-open, lateral approach in the thoracic and lumbar spine. *Spine* 2010;35:S338-S346.
 703. Thordarson DB. Facilitating edema resolution with a foot pump after calcaneus fracture. *J Orthop Trauma* 1998;13:43-6.
 704. Thumbikat P, Poonnoose PM, Balasubrahmaniam P, et al. A comparison of heparin/warfarin and enoxaparin thromboprophylaxis in spinal cord injury: The Sheffield experience. *Spinal Cord* 2002;40:416-20.
 705. Turpie AGG, Bauer KA, Eriksson BI, et al. Superiority of fondaparinux over enoxaparin in preventing venous thromboembolism in major orthopedic surgery using different efficacy end points. *CHEST* 2004; 126:501-8.
 706. Vallier HA, Cureton BA, Ekstein C, et al. Early definitive stabilization of unstable pelvis and acetabulum fractures reduces morbidity. *J Trauma Inj Infect Crit Care* 2010;69:677-684.
 707. Wille-Jorgensen P, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome: A systematic review and meta-analysis. *Thromb Haemost* 2005; 93:236-41.
 708. Yadla, S.; Malone, J.; Campbell, P. G.; Maltenfort, M. G.; Harrop, J. S.; Sharan, A. D.; Ratliff, J. K.
- Excluded because the study was not controlled (n=9)
709. Cullison TR, Muldoon MP, German JD, et al. The incidence of deep venous thrombosis in anterior cruciate ligament reconstruction. *Arthroscopy* 1996;12:657-9.
 710. Gerlach R, Raabe A, Beck J, et al. Postoperative nadroparin administration for prophylaxis of thromboembolic events is not associated with an increased risk of hemorrhage after spinal surgery. *European Spine Journal* 2004;13:9-13.
 711. Hara N, Minami T. Diffusive pulmonary embolism with bone fragments during spinal surgery [7]. *Br J Anaesth* 2006;97:119-20.
 712. Hönemann CW, Brodner G, Van Aken H, et al. Aortic perforation during lumbar laminectomy. *Anesth Analg* 1998;86:493-5.
 713. Quinn RH, Drenga J. Perioperative morbidity and mortality after reconstruction for metastatic tumors of the

proximal femur and acetabulum. *J Arthro* 2006; 21(2):227-32.

714.Saragaglia D, Blaysat M, Inman D, et al. Outcome of opening wedge high tibial osteotomy augmented with a Biosorb® wedge and fixed with a plate and screws in 124 patients with a mean of ten years follow-up. *Int Orthop* 2010;1-6

715.Shah AK, Moreno-Aspitia A. Acquired factor V inhibitor and single exposure to autologous growth factor. *Thromb Res* 2005;116:87-9.

716.Smith JS, Fu KMG, Polly DW, et al. Complication rates of three common spine procedures and rates of thromboembolism following spine surgery based on 108,419 procedures: A report from the scoliosis research society morbidity and mortality committee. *Spine* 2010;35:2140-2149.

717.Solis G, Saxby T. Incidence of DVT following surgery of the foot and ankle. *Foot Ankle Int* 2002; 23(5):411-14.

Excluded because the study did not evaluate a comparison of interest (n=27)

718.Camporese G, Bernardi E, Prandoni P, Noventa F, Verlato F, Simioni P, Ntita K, Salmistraro G, Frangos C, Rossi F, Cordova R, Franz F, Zucchetta P, Kontothanassis D, Andreozzi GM. KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group. *Ann Intern Med* 2008;149:73-82.

719.Ferree BA, Wright AM. Deep venous thrombosis following posterior lumbar spinal surgery. *Spine* 1993;18:1079-82.

720.Gehling H, Giannadakis K, Lefering R, et al. [Prospective randomized pilot study of ambulatory prevention of thromboembolism. 2 times 500 mg aspirin (ASS) vs. clivarin 1750 (NMH)]. *Unfallchirurg* 1998;101:42-9.

721.Kim HJ, Kepler C, Cunningham M, et al. Pulmonary embolism in spine surgery: A comparison of combined anterior/posterior approach versus posterior approach surgery. *Spine* 2011;36:177-179.

722.Kock HJ, Schmit NKP, Hanke J, et al. Patient compliance during low molecular weight heparin thromboprophylaxis in outpatients with plaster cast immobilisation of the leg. *Unfallchirurgie* 1994;20:319-28.

723.Kock HJ, Schmit-Neuerburg KP, Hanke J, et al. [Ambulatory prevention of thrombosis with low molecular weight heparin in plaster immobilization of the lower extremity]. *Chirurg* 1993;64:483-91.

724.Kock HJ, Schmit-Neuerburg KP, Hanke J, et al. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;346:459-61.

725.Kock HJ, Schmit-Neuerburg KP, Hanke J, et al. [Implementing ambulatory prevention of thrombosis with low molecular weight heparin in plaster immobilization of the lower extremity]. *Unfallchirurgie* 1994;20:319-28.

726.Kock HJ, SchmittNeuerburg KP, Hanke J, et al. Prophylaxis of venous thromboembolism with low molecular weight heparin in surgical outpatients with immobilization of the lower limb by plaster cast. *Hamostaseologie* 1993;13:S36-9.

727.Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. *Haemostasis* 1993;23:20-6.

728.Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop* 2007;78:528-35.

729.Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;347:726-30.

730.Ma Y, Passias P, Gaber-Baylis LK, et al. Comparative in-hospital morbidity and mortality after revision versus primary thoracic and lumbar spine fusion. *Spine J* 2010;10:881-889.

731.Marlovits S, Striessnig G, Schuster R, et al. Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study. *Arthroscopy* 2007;23:696-702.

732.Misselwitz F, Wirth T, Tuytu H, et al. Prevention of venous thromboembolism after knee arthroscopy. Combined data of a randomised controlled trial and a large outpatient cohort treated with reviparin. *Ann Hematol* 2002;81:A57

733.Motycka T, Eggerth G, Landsiedl F. The incidence of thrombosis in high tibial osteotomies with and without the use of a tourniquet. *Arch Orthop Trauma Surg* 2000;120:157-9.

734.Nasser R, Yadla S, Maltenfort MG, et al. Complications in spine surgery a review. *J Neurosurg Spine* 2010;13:141-143.

735.Nelson LD,Jr, Montgomery SP, Dameron TB,Jr, et al. Deep vein thrombosis in lumbar spinal fusion: a prospective study of antiembolic and pneumatic compression stockings. *J South Orthop Assoc* 1996;5:181-4.

736.Normand R, Mathieu JP. [Prevention of venous thromboses under plaster casts after leg injury. Comparison of

heparin-calcium and pentosan sulfuric polyester]. <i>Cah Anesthesiol</i> 1987;35:559-62.
737.Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. <i>Spine</i> 1996;21:853-9.
738.Roth VP. Prophylaxis of deep vein thrombosis in outpatients undergoing arthroscopic menisci operation. <i>Orthopadische Praxis</i> 1995; 5:345-8.
739.Smith TO, Hing CB. The efficacy of the tourniquet in foot and ankle surgery? A systematic review and meta-analysis. <i>Foot and Ankle Surgery</i> 2010;16:3-8.
740.Smith TO, Hing CB. A meta-analysis of tourniquet assisted arthroscopic knee surgery. <i>Knee</i> 2009;16:317-21.
741.SooHoo NF, Eagan M, Krenek L, et al. Incidence and factors predicting pulmonary embolism and deep venous thrombosis following surgical treatment of ankle fractures. <i>Foot Ankle Surg</i> 2010.
742.Spannagel U, Kujath P. Low molecular weight heparin for the prevention of thromboembolism in outpatients immobilized by plaster cast. <i>Semin Thromb Hemost</i> 1993;19:131-41.
743.Wirth T, Schneider B, Misselwitz F, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. <i>Arthroscopy</i> 2001;17:393-9.
744.Wood KB, Kos PB, Abnet JK, et al. Prevention of deep-vein thrombosis after major spinal surgery: A comparison study of external devices. <i>J Spinal Disord</i> 1997;10:209-14.
Excluded because the study did no report an outcome of interest (n=4)
745.Ahmad S, Bacher HP, Lassen MR, et al. Investigations of the immunoglobulin subtype transformation of anti-heparin-platelet factor 4 antibodies during treatment with a low-molecular-weight heparin (clivarin) in orthopedic patients. <i>Arch Pathol Lab Med</i> 2003;127:584-8.
746.Stöckle U, Hoffmann R, Raschke M, et al. Intermittent impulse compression. A new method of reducing post-traumatic and postoperative edema. <i>Chirurg</i> 1996;67:539-45
747.Stöckle U, Hoffmann R, Schütz M, et al. Fastest reduction of posttraumatic edema: Continuous cryotherapy or intermittent impulse compression? <i>Foot and Ankle International</i> 1997;18:432-8.
748.Thordarson DB, Ghahambor N, Perlman M. Intermittent pneumatic pedal compression and edema resolution after acute ankle fracture: A prospective, randomized study. <i>Foot and Ankle International</i> 1997;18:347-50.

Appendix D. Quality and Characteristics of Included Trials and Studies

Table 3. Quality and characteristics of randomized controlled trials in major orthopedic surgery

Study, year	Trial characteristics	Population and interventions	Followup and Outcomes of interest (Timing)	Quality assessment
Yokote, 2011	<p>Publication type: Full text</p> <p>Geographic location: Japan</p> <p>Funding: Unknown</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomly assigned to either of the three groups</p> <p>Outcome assessment: Ultrasonographic scans performed by experienced vascular technicians and were read by experienced radiologists who were blinded to the patient's randomization</p> <p>Total number randomized: 255 (255)</p>	<p>Inclusion criteria: Primary, unilateral THR</p> <p>Exclusion criteria: Bilateral and revision THR; <20 years; long term anticoagulant treatment such as UFH, LMWH, VKA, antiplatelet agents; pre-existing cardiac or cerebrovascular disease; history of VTE, coagulation disorder including ant-phospholipids syndrome; presence of a solid malignancy tumor or peptic ulcer; major surgery in the preceding 3m; Caucasian patients</p> <p>Intervention 1: Fondaparinux 2.5mg SQ starting at a mean of 18h post-operatively the daily for 10 consecutive days</p> <p>Intervention 2: Enoxaparin 20mg BD or 40mg SQ starting at a mean of 17h post-operatively then daily for 10 consecutive days</p> <p>Comparator: Placebo (saline injections)</p>	<p>Duration of followup: 84 days post-operative</p> <p>Followup: Fondaparinux 98.8% Enoxaparin 97.6% Placebo 97.6%</p> <p>Final: Symptomatic VTE, PE, fatal PE, nonfatal PE (11d); mortality, mortality due to bleeding (84d)</p> <p>Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (11d)</p> <p>Adverse events: Major bleeding, minor bleeding (11d)</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Partially</p> <p>4. Were outcome assessors blind to exposure/intervention status? Partially</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Fair</p>
Fuji, 2010	<p>Publication type: Full text</p>	<p>Inclusion criteria: Age ≥20y; weight ≥40kg; primary, unilateral elective TKA; signed, informed consent</p>	<p>Duration of followup: post-operative</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic</p>

Chin, 2009	Geographic location: Japan	Exclusion criteria: Any bleeding diathesis; major surgery, trauma, uncontrolled HTN, MI in last 3m; clinically relevant bleeding, gastric/duodenal ulcer in last 6m; hx hemorrhagic stroke or acute intracranial bleeding; hx VTE or preexisting condition requiring anticoagulant therapy; severe liver disease or elevated AST or ALT >2xULN; significant renal disease; treatment with anticoagulants, antiplatelet agents, or NSAIDs with a half-life of >12h within 7d before TKA; anticipated requirement for IPC of lower limb; pregnancy, women of child-bearing potential; hx TCP; previous leg amputation; active malignant disease	Followup: Dabigatran 150mg 82.54%; 220mg 74.42%; placebo 81.45%	factors? Yes
	Funding: Industry		Final: Major VTE, PE, fatal PE, nonfatal PE, mortality, mortality due to bleeding (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 38		Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: Randomized into 4 treatment groups using a computer-generated scheme stratified by study center in block of 4		Adverse events: Major bleeding, minor bleeding, major bleeding leading to reoperation, bleeding leading to transfusion (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Outcome assessment: Diagnostic tests for VTE were evaluated centrally by an independent adjudication committee blinded to treatment allocation, two medical experts reviewed all cases of bleeding	Intervention 1: Dabigatran 150mg po at least 2h after removing indwelling catheter + confirming absence of abnormal bleeding at drainage site, 150mg 8h+ after first dose then QD at 8AM for 11-14d postoperatively		5. Were the methods used for randomization adequate? Yes
	Total number randomized: 512 (379)	Intervention 2: Dabigatran 220mg po at least 2h after removing indwelling catheter and confirming absence of abnormal bleeding at drainage site, 220mg 8h or more after the first dose, then QD at 8AM for 11-14d postoperatively		6. Were methods for allocation concealment adequate? Yes
		Comparator: Placebo capsules		7. Were incomplete outcome data adequately addressed? Yes
	Publication type: Full text	Inclusion criteria: Elective TKA; low-risk patients and those without predisposition to thromboembolism	Duration of followup: Post-operative	8. Was intention to treat analysis used? Yes
	Geographic location: Singapore	Exclusion criteria: Use of anticoagulants or aspirin; history of PE or DVT in the previous year; obesity; pre-operative prolonged immobilization or wheelchair bound; bleeding tendency or a	Followup: 100% in all arms	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Funding: NR		Final: PE (post-operative)	10. Was the overall loss to followup low (< 20%)? No
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Good

	Number of centers: 1	history of GI bleeding; surgery in the previous 6m; CVA in the previous 3m; uncontrolled HTN; CHF; renal or liver impairment; allergy to heparin or HIT; varicose veins or CVI; PVD; skin ulcers; dermatitis or wounds; malignancy	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	participants? Partially
	Randomization and allocation concealment: NR		Adverse events: Bleeding complications (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Bilateral DUS was carried out by ultrasonographers blinded to the prophylactic method used	Intervention: Enoxaparin 40mg/d SQ started postoperatively until 5-7d or if DVT or PE suspected		5. Were the methods used for randomization adequate? Can't tell
	Total number randomized: 440 (220)	Comparator: Control		6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Fair
Ginsberg, 2009	Publication type: Full text	Inclusion criteria: ≥18y and >40 kg, scheduled for primary elective unilateral TKA	Duration of followup: 90d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
RE-MOBILIZE	Geographic location: Canada, Mexico, USA, UK	Exclusion criteria: Known inherited or acquired clinically significant bleeding disorder; major surgery, trauma, uncontrolled HTN or MI < 3m; hx of acute intracranial disease or hemorrhagic stroke; GI or urogenital bleeding or ulcer disease < 6m; severe liver disease; ALT or AST > 2X ULN range < last m; severe renal insufficiency; concomitant long acting NSAID therapy or anticoagulant during study drug treatment; active malignant disease; platelet count < 100 × 10 ⁹ /L; pregnant; nursing, or premenopausal women of child-bearing potential who were not practicing effective birth control; failure to provide informed consent	Followup: 100% in all arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry		Final: Mortality due to bleeding, mortality (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 97		Intermediate: Symptomatic DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly assigned to 1 of 3 treatment groups after surgery using an Interactive Voice Response System in blocks of 6 based on an independently generated scheme		Adverse events: Major bleeding, minor bleeding (post-operative during study period, post	5. Were the methods used for randomization adequate? Yes
				6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes

Edwards, 2008	Outcome assessment: Diagnostic tests for VTE events were initially evaluated locally, subsequently reviewed by an independent central adjudication committee blinded to treatment allocation. An independent expert adjudication committee classified all bleeding events	Intervention 1: Dabigatran 75mg PO starting 6-12h post-operative followed by 150mg PO QD for a total duration of 12-15d post-operative	study period-90d); major bleeding leading to re-operation, surgical site bleeding (post-operative during study period)	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
		Intervention 2: Dabigatran 110mg PO starting 6-12h post-operative followed by 220mg PO QD for a total duration of 12-15d post-operative		10. Was the overall loss to followup low (< 20%)? Yes
	Total number randomized (number randomized in arms of interest): 2615 (2615)	Intervention 3: Enoxaparin 30mg SQ BID starting 12-24h post-operative for a total duration of 12-15d post-operative		11. Conflict of interest reported and insignificant? Yes
	Publication type: Full text	Inclusion criteria: Patients undergoing THA or TKA	Duration of followup: 90d	Overall quality rating: Good
	Geographic location: USA	Exclusion criteria: Protocol violations such as missed ultrasound; surgery other than THA or TKA; previous history of thrombosis; prophylaxis other than LMWH	Followup: 100% in all arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry		Final: PE, fatal PE, nonfatal PE (90d); mortality, mortality due to bleeding (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: NR	Intervention: Enoxaparin 30 mg Q12h SQ from the morning after surgery until 7-8 th post-operative day + IPC (ActiveCare DVT) on the calves of the patients in the operation room and worn until discharge	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: NR			4. Were outcome assessors blind to exposure/intervention status? Partially
	Outcome assessment: Diagnosis of PE was adjudicated by a separate committee	Comparator: Enoxaparin 30 mg Q12h SQ from the morning after surgery until 7-8 th post-operative day	Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Total number randomized: 277 (277)			6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes

				11. Conflict of interest reported and insignificant? Yes
Fuji, 2008 THA	Publication type: Full text	Inclusion criteria: Primary elective THA; ≥20y	Duration of followup: Post-operative	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Partially 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Geographic location: Japan Funding: Industry Number of centers: 51 Randomization and allocation concealment: 1:1 ratio Outcome assessment: Objective tests for DVT and PE were centrally adjudicated by an independent expert panel blinded to treatment group; intra-abdominal or intracranial bleeding confirmed by US, CT, or MRI Total number randomized: 421 (421)	Exclusion criteria: Revision THA; CI to heparin therapy; positive clinical evidence of chronic postphlebotic syndrome or acute DVT within 12m of study drug treatment; allergy to iodine or contrast medium; CrCl <30 mL/min or plasma Cr level >1.5mg/dl; severe hepatic disease; uncontrolled HTN; illicit drug use of alcohol abuse; treatment with other investigation agents within 3m of surgery; failure to achieve post-operative hemostasis; females if pregnant or breastfeeding Intervention 1: Enoxaparin 40mg SQ daily starting 24-36h postoperatively for 14d Intervention 2: Enoxaparin 20mg SQ BID starting 24-36h postoperatively for 14d Comparator: Placebo (saline) injections	Followup: Enoxaparin 40mg 74.8%; enoxaparin 20mg 85.7%; placebo 81.9% Final: PE (postoperative) Intermediate: DVT, proximal DVT (post-operative) Adverse events: Major bleeding, minor bleeding (post-operative)	
Fuji, 2008 TKA	Publication type: Full text	Inclusion criteria: Primary TKA; ≥20y	Duration of followup: Post-operative	Overall quality rating: Good 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria?
	Geographic location: Japan	Exclusion criteria: Revision TKA; CI to heparin therapy; positive clinical evidence of chronic postphlebotic	Followup: Enoxaparin 40mg 78.7%; enoxaparin 20mg 84.8%;	

	Funding: Industry	syndrome or acute DVT within 12m of study drug treatment; allergy to iodine or contrast medium; CrCL <30 mL/min or plasma Cr >1.5 mg/dL; severe hepatic disease; uncontrolled HTN; illicit drug use of alcohol abuse; treatment with other investigation agents within 3m of surgery; failure to achieve post-operative hemostasis; females if pregnant or breastfeeding	placebo 82.3%	Yes
	Number of centers: 51		Final: PE (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: 1:1 ratio		Intermediate: DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Outcome assessment: Objective tests for DVT and PE were centrally adjudicated by an independent expert panel blinded to treatment group; intra-abdominal or intracranial bleeding confirmed by US, CT, or MRI	Intervention 1: Enoxaparin 40mg SQ daily starting 24-36h postoperatively for 14d Intervention 2: Enoxaparin 20mg SQ BID starting 24-36h postoperatively for 14d Comparator: Placebo (saline) injections	Adverse events: Major bleeding, minor bleeding (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Total number randomized: 382 (382)			6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used?
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Thorey, 2008	Publication type: Full text	Inclusion criteria Patients undergoing simultaneous bilateral cemented TKA	Duration of followup: 180d	Overall quality rating: Good
	Geographic location: Germany	Exclusion criteria History of DVT; musculoskeletal infection in the lower extremities; bleeding diathesis; neurological problems; PVD	Followup: 100%	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Unknown	Intervention 1: Tourniquet release and hemostasis before wound closure	Final: NR	2. Were outcomes assessed using a valid methodology and criteria? Can't tell
	Number of centers: 1	Intervention 2: Tourniquet release after wound closure and pressure dressing	Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (180d)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: NR		Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Can't tell
				5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data

	Outcome assessment: NR			adequately addressed? Yes
	Total number randomized (number randomized in arms of interest): 20 (20)			8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Poor
Eriksson, 2007a RE- MODEL	Publication type: Full text	Inclusion criteria ≥18y and >40 kg, scheduled for primary elective unilateral TKA	Duration of followup: 90d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Poland, Netherlands, South Africa, Spain, Sweden	Exclusion criteria Any bleeding diathesis; hx of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled HTN or MI within the past 3m; GI or urogenital bleeding or ulcer disease within the past 6m; severe liver disease; AST or ALT levels >2 X ULN range within the past m; severe renal insufficiency; concomitant long-acting NSAID therapy; active malignant disease; and being female and of childbearing potential	Followup: Dabigatran 150mg 88.90% Dabigatran 220mg 89.4% Enoxaparin 88.76%	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry		Final: Major VTE, fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 105		Intermediate: Asymptomatic DVT, symptomatic DVT (post- operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly assigned using a computer-generated central scheme stratified by study center in blocks of 6	Intervention 1: Dabigatran 75mg PO starting 1-4h post- operative followed by 150mg PO QD for 6- 10d post-operative		5. Were the methods used for randomization adequate? Yes
		Intervention 2: Dabigatran 110mg PO starting 1-4h post- operative followed by 220mg PO QD for 6- 10d post-operative		6. Were methods for allocation concealment adequate? Yes
	Outcome assessment: All VTE and bleeding events reviewed by an independent central adjudication committee blinded to treatment allocation	Intervention 3: Enoxaparin 40mg SQ QD starting evening before surgery (post-operative in some countries) for 6-10d post-operative	Adverse events: Major bleeding, minor bleeding, major bleeding leading to re-operation, bleeding leading to transfusion (post-operative)	7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Good

Eriksson, 2007b RE-NOVATE	Total number randomized (number randomized in arms of interest): 2101 (2101)			
	Publication type: Full text	Inclusion criteria ≥18 y, ≥40 kg scheduled for primary elective unilateral THR	Duration of followup: 94d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
RE-NOVATE	Geographic location: Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, South Africa, Spain, Sweden	Exclusion criteria Any bleeding diathesis; hx of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled HTN, or MI in the past 3m; GI or urogenital bleeding, or ulcer disease in the past 6m; severe liver disease; ALT or AST concentrations >2X ULN range in the past m; severe renal insufficiency; use of long-acting NSAID; childbearing potential; allergy to radiopaque contrast media or heparin; and active malignant disease; > 3 attempts or traumatic placement of spinal or epidural anesthesia	Followup: 100% in all arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry		Final: Major VTE, fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 115		Intermediate: Asymptomatic DVT, symptomatic DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly assigned stratified by study center with a central computer generated scheme in blocks of 6, with the lowest number allocated sequentially	Intervention 1: Dabigatran 75mg PO starting 1-4h post-operative followed by 150mg PO QD for 28-35d post-operative until venography	Adverse events: Major bleeding, minor bleeding, major bleeding leading to re-operation, bleeding leading to transfusion (post-operative)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: Diagnostic tests for VTE events were initially assessed locally, then by an independent central adjudication committee blinded to treatment allocation. Bleeding outcomes classified by an independent, expert adjudication committee	Intervention 2: Dabigatran 110mg PO starting 1-4h post-operative followed by 220mg PO QD for 28-35d post-operative until venography		6. Were methods for allocation concealment adequate? Yes
		Intervention 3: Enoxaparin 40mg SQ QD starting evening before surgery (post-operative in some countries) for 28-35d post-operative until venography		7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
	Total number randomized (number randomized in arms of interest):			Overall quality rating: Good

Lassen, 2007	3494 (3494)			
	Publication type: Full text	Inclusion criteria: 18-90y; scheduled for TKR	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Argentina, Australia, Canada, Mexico, Denmark, Israel, Poland, USA	Exclusion criteria: Female w/child-bearing potential; bleeding/coagulation disorders; history of HIT; intracranial/ intraocular hemorrhage w/in past 5y; GI bleeding, brain, spinal, ophthalmologic or major surgery/trauma w/in 90d of surgery; ulcer disease w/in 30d before surgery; known VTE disease w/in past 12m; uncontrolled HTN, wound or other bleeding; malignant disease; active hepatobiliary disease; known or suspected GI disease that may affect absorption of study medication; ALT, AST or bilirubin >1.5 ULN; INR >1.4 or APTT >1.4 control; hypersensitivity to UFH, LMWH, VKA, porcine products or iodinated venography contrast medium; treatment with medications affecting coagulation/platelet function w/in 7d prior to surgery; traumatic or difficult lumbar puncture; use of epidural or intrathecal catheter post-operative	Followup: 100% in all arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR		Final: Fatal PE, non-fatal PE, mortality, mortality due to bleeding (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Partially
	Number of centers: 97		Intermediate: Asymptomatic DVT, symptomatic DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Computer-generated allocation		Adverse events: Major bleeding, minor bleeding (post-operative)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: Efficacy, bleeding events and cause of death were adjudicated by an independent central committee unaware of treatment assignments			6. Were methods for allocation concealment adequate? Yes
	Total number randomized (number randomized in arms of interest): 1238 (458)	Intervention 1: Enoxaparin 30mg SQ Q12h 12-24h after skin wound closure then Q12h for 12 ± 2d Intervention 2: Warfarin 5mg PO daily in evening starting evening of surgery for 12 ± 2d		7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Good
Bonneux, 2006	Publication type: Full text	Inclusion criteria: Disabling knee conditions requiring TKA or revision of at least one of the metal components of previous TKA	Duration of followup: 42d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Belgium	Exclusion criteria: Known hypersensitivity to enoxaparin sodium, fondaparinux or to any of the excipients, heparin, pork products; infectious	Followup: 90.83% overall	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR		Final: NR	3. Were subjects and providers blind to the intervention status of

	Number of centers: 1	arthritis; acute bacterial endocarditis; severe renal impairment; active ulcerative GI disease; active clinically significant bleeding; congenital or acquired bleeding disorder; recent intracranial hemorrhage; shortly after brain, spinal or ophthalmic surgery; low body weight (<50kg); suspicion of infection of previous TKA	Intermediate: Symptomatic DVT (post-operative)	participants? No
	Randomization and allocation concealment: Randomized using a computer program		Adverse events: Re-operation (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Outcome assessment: NR	Intervention 1: Fondaparinux 2.5mg QD starting 6-12h post-operative for a duration of 6wks		5. Were the methods used for randomization adequate? Yes
	Total number randomized (number randomized in arms of interest): 120 (120)	Intervention 2: Enoxaparin 40mg QD starting evening before surgery for a duration of 6wks postoperatively		6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Can't tell
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Senaran, 2006	Publication type: Full text	Inclusion criteria: ≥18y scheduled for THA	Duration of followup: 42d	Overall quality rating: Fair
	Geographic location: Turkey	Exclusion criteria: Hx of blood dyscrasia, HIT; allergy to enoxaparin or heparin that would preclude anticoagulant therapy	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry		Final: Symptomatic objectively confirmed VTE (post-operative until discharge, discharge-42d); fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (42d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Intervention 1: Enoxaparin 40mg SQ QD starting 12h before surgery for a duration of 7-10d post-operative or until discharge		3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: Randomized to either treatment groups	Intervention 2: Heparin 5000 IU SQ q8h starting 12h before surgery for a duration of 7-10d post-operative or until discharge	Intermediate: DVT (post-operative until discharge, discharge-42d)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Outcome assessment:			5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes

NR

Total number randomized
(number randomized in arms of
interest):
100 (100)

Adverse events:
Major bleeding, minor
bleeding, surgical site
bleeding, HIT, re-admission
(post-operative)

8. Was intention to treat analysis
used? Yes
9. Was the differential loss to
followup between the compared
groups low (< 10%)? Yes
10. Was the overall loss to
followup low (< 20%)? Yes
11. Conflict of interest reported and
insignificant? Yes

Overall quality rating: Fair

Westrich,
2006

Publication type:
Full text

Inclusion criteria:
Patients undergoing primary TKA

Duration of followup:
Post-operative

1. Were the groups similar at
baseline in terms of baseline
characteristics and prognostic
factors? Yes
2. Were outcomes assessed using
a valid methodology and criteria?
Yes
3. Were subjects and providers
blind to the intervention status of
participants? No
4. Were outcome assessors blind
to exposure/intervention status?
Can't tell
5. Were the methods used for
randomization adequate? Can't tell
6. Were methods for allocation
concealment adequate? Can't tell
7. Were incomplete outcome data
adequately addressed? Yes
8. Was intention to treat analysis
used? Yes
9. Was the differential loss to
followup between the compared
groups low (< 10%)? Yes
10. Was the overall loss to
followup low (< 20%)? Yes
11. Conflict of interest reported and
insignificant? No

Geographic location:
USA

Exclusion criteria:
History of previous thromboembolism;
patients undergoing revision arthroplasty;
patients taking Coumadin preoperatively for
other medical reasons

Followup:
100% in both arms

Funding:
Unknown

Final:
NR

Number of center:
1

Intervention 1:
Procedure modified to minimize the total
amount of time the knee was hyperflexed
and dislocated, the knee was extended
during preparation of the femoral and tibial
sides not to allow the knee to be in the flexed
state for more than 4 min

Intermediate:
DVT, proximal DVT (post-
operative)

Randomization and allocation
concealment:
Patients were divided into two
groups using random numbers

Adverse events:
NR

Outcome assessment:
NR

Intervention 2:
Procedure according to normal protocol,
which kept the knee in extreme flexion and
maintained dislocation for the duration of the
exposure, as in a standard knee replacement
(i.e., extended only after the trial components
were inserted and the patella to be cut)

Total number randomized
(number randomized in arms of
interest):
118 (118)

Eriksson, 2005 BISTRO II	Publication type: Full text	Inclusion criteria: ≥18y, ≥40 kg scheduled for primary elective THR or TKR	Duration of followup: 28-42d	Overall quality rating: Poor 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Geographic location: Austria, Belgium, Czech Republic, Denmark, Finland, France, Hungary, Italy, Netherlands, Norway, South Africa, Sweden Funding: Industry Number of centers: 60 Randomization and allocation concealment: Assigned randomly to 5 treatment groups, stratified by the study center and surgical procedure (hip or knee replacement), using a computer-generated scheme Outcome assessment: All tests for VTE during the treatment period were first evaluated locally and subsequently by an independent central adjudication committee blinded to the treatment allocation. A centralized independent committee classified all bleeding events Total number randomized (number randomized in arms of interest): 1973 (1973)	Exclusion criteria: Any bleeding diathesis; coagulation disorders; hx of or acute intracranial disease; major surgery or trauma within the last 3m; CVD including uncontrolled HTN or hx of MI within the last 6m; hx of stroke; DVT, GI or pulmonary bleeding within the last year; known liver; renal disease; use of long-term anticoagulants, antiplatelet drugs (except low-dose aspirin up to 160 mg daily), or fibrinolytics within 7d prior to surgery; allergy to radiopaque contrast media; TCP; active malignant disease; current cytostatic treatment or recent treatment with an investigational drug; women of childbearing potential; those with leg amputations and known alcohol or drug abuse Intervention1: Dabigatran 50mg PO BID Intervention 2: Dabigatran 150mg PO BID Intervention 3: Dabigatran 300mg PO QD Intervention 4: Dabigatran 225mg PO BID All dabigatran doses started within 1-4h post-operative and continued until venography (6-10d) Intervention 5: Enoxaprin 40mg SQ QD starting 12h before	Followup: 100% in all arms Final: VTE (post-operative) Intermediate: Proximal DVT, distal DVT (post-operative) Adverse events: Major bleeding (post-operative)	
				Overall quality rating: Good

surgery and continued until venography (6-10d)

Farag, 2005	Publication type: Full text	Inclusion criteria: Patients scheduled for TKR	Duration of followup: 10d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to exposure/intervention status? Can't tell 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No Overall quality rating: Fair
	Geographic location: USA Funding: Unknown Number of centers: 1 Randomization and allocation concealment: Patients were randomized using cards generated from a computer-generated random number list into two groups Outcome assessment: NR Total number randomized (number randomized in arms of interest): 38 (38)	Exclusion criteria: In the epidural group, patients were excluded from the study if the epidural catheter could not be placed or maintained for the full study interval Intervention 1: Spinal anesthesia: 0.5% bupivacaine and analgesia with intravenous morphine via patient-controlled analgesia demand mode only Intervention 2: Epidural anesthesia: 1.0% ropivacaine with 1:200000 epinephrine and analgesia with 0.2% ropivacaine at 8 mL/h, maintained for 7d	Followup: 100% in both arms Final: NR Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (10d) Adverse events: NR	
Lachiewicz, 2004	Publication type: Full text	Inclusion criteria: Patients who had undergone primary or revision TKA	Duration of followup: 180d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers
	Geographic location: USA Funding: Industry	Exclusion criteria: Hemophilia; allergy to aspirin; removal of an infected knee arthroplasty	Followup: 100% in both arms Final: Fatal PE, nonfatal PE, PE,	

	<p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomized using sealed envelopes</p> <p>Outcome assessment: Ultrasonography of the calf and thigh, as far cranially as the inguinal ligament, was performed by experienced vascular technicians who were blinded to treatment allocation</p> <p>Total number randomized (number randomized in arms of interest): 423 (423)</p>	<p>Intervention 1: IPC (Venaflow) applied to contralateral limb in operating room before the procedure and operated limb at the end of the procedure and worn continuously for at least 12 – 16h/d except for bathing and physiotherapy</p> <p>Intervention 2: IPC (Kendal) applied to contralateral limb in operating room before the procedure and operated limb at the end of the procedure and worn continuously for at least 12 – 16h/d except for bathing and physiotherapy</p>	<p>mortality, mortality due to bleeding (postoperative)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (postoperative); symptomatic DVT (discharge-180d)</p> <p>Adverse events: NR</p>	<p>blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Good</p>
Silbersack, 2004	<p>Publication type: Full text</p> <p>Geographic location: Germany</p> <p>Funding: Industry</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomly assigned to either group</p> <p>Outcome assessment: Duplex ultrasonography performed by a independent angiologist unaware of the</p>	<p>Inclusion criteria: Patients >18y awaiting primary unilateral THR or TKR</p> <p>Exclusion criteria: History of cardiac insufficiency (NYHA III/IV); stage III chronic renal insufficiency; severe peripheral arterial disease; acute thrombophlebitis; neurological disorders or arthrodeses of lower limb; recent anticoagulation; hemorrhagic diathesis; allergy to heparins; active malignant disease</p> <p>Intervention 1: Enoxaparin 40mg SQ daily, starting evening prior to surgery and continued until 30d post-operative + IPC (Venaflow) bilaterally after operation in the recovery room and worn continuously until post-operative day 10 whenever the patient is in bed</p> <p>Intervention 2:</p>	<p>Duration of followup: 84d</p> <p>Followup: 100% in both arms</p> <p>Final: PE, fatal PE, nonfatal PE (42-84th post-operative days)</p> <p>Intermediate: DVT, proximal DVT; distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to</p>

	method of prophylaxis	Enoxaparin 40mg SQ daily, starting evening prior to surgery and continued until 30d post-operative + GCS (Comprinnet Pro) bilaterally after operation for a maximum of 90d if without thromboembolic complications		followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
Eriksson, 2003	<p>Total number randomized (number randomized in arms of interest): 131 (131)</p> <p>Publication type: Full text</p> <p>Geographic location: Europe and South America</p> <p>Funding: Industry</p> <p>Number of centers: Multicenter</p> <p>Randomization and allocation concealment: computer-generated randomization list balanced in blocks of equal numbers and stratified by center</p> <p>Outcome assessment: All efficacy outcomes and the safety outcomes bleeding and death were adjudicated by a central independent committee, the members of which were unaware of the patients' treatment assignment</p> <p>Total number randomized (number randomized in arms of interest): 656 (656)</p>	<p>Inclusion criteria: ≥18y old; undergoing standard surgery for fracture of the upper third of the femur, including femoral head and neck; surgery planned within 48h after admission</p> <p>Exclusion criteria: Trauma affecting more than 1 organ system or if more than 24h had elapsed between the causative trauma and hospital admission; active bleeding; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic GI disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery < 3m; difficulty in performing epidural or spinal anesthesia; planned indwelling intrathecal or epidural catheter >6h after surgery; contraindication to anticoagulant therapy; pregnancy; hypersensitivity to contrast media; SCr> 2.0 mg/dL in a well-hydrated patient; long-term anticoagulant treatment for a chronic comorbid condition; receiving any type of anticoagulant or fibrinolytic therapy or dextran from admission to first study drug administration or surgery</p> <p>Intervention 1: Fondaparinux 2.5mg SQ started <2h after randomization, then continued QD for 25-31d</p> <p>Intervention 2: Fondaparinux 2.5mg SQ QD started <2h after randomization, continued for 6-8d after surgery, then placebo 19-23d</p>	<p>Duration of followup: 32d</p> <p>Followup: 100% in both arms</p> <p>Final: VTE, fatal PE, nonfatal PE, PE, mortality (32d)</p> <p>Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (32d)</p> <p>Adverse events: Major bleeding, minor bleeding, major bleeding leading to re-operation, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion (32d)</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Good</p>
Kim, 2003	Publication type:	Inclusion criteria:	Duration of followup:	1. Were the groups similar at

	Full text	Patients who had primary THR	180d	baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Korea	Exclusion criteria: NR	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Unknown	Intervention 1: Cemented replacement	Final: NR	3. Were subjects and providers blind to the intervention status of participants? Can't tell
	Number of centers: 1	Intervention 2: Uncemented replacement	Intermediate: DVT, proximal DVT; distal DVT (180d)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: Randomization between cemented and cementless replacements in both groups was determined from a sequential pool maintained by statisticians, based on a table of randomized numbers		Adverse events: NR	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: NR			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 200 (200)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair
Lassen, 2002	Publication type: Full text	Inclusion criteria: ≥18y scheduled for primary elective THR, or revision of at least one component of a previously implanted total hip prosthesis	Duration of followup: 49d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: 16 European countries	Exclusion criteria: Bilateral hip surgery planned during the same procedure or within 2wks after inclusion. active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; haemorrhagic stroke or brain, spinal, or ophthalmological surgery within previous 3m; planned indwelling intrathecal	Followup: Fondaparinux: 78.6% Enoxaparin: 79.6%	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry		Final: Symptomatic objectively confirmed VTE, mortality, nonfatal PE, fatal PE (49d); mortality due to bleeding (11d)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 73			4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation			5. Were the methods used for

	<p>concealment: Blocks of four by a computer generated randomization list</p> <p>Outcome assessment: Efficacy outcomes, including review of all venograms, bleeding, and death were judged by a central independent committee, unaware of the patients' treatment assignment</p> <p>Total number randomized (number randomized in arms of interest): 2309 (2309)</p>	<p>or epidural catheter > 6h after end of surgery; hypersensitivity to heparin, LMWHs, porcine products, or iodinated contrast media; CI to anticoagulant treatment; concomitant intake of any drug that could not be combined with contrast media; addictive disorders; SCr >180 mmol/L in a well-hydrated patient; and platelet <100X10⁹/L; patients who needed anticoagulant treatment or who had received any type of anticoagulant or fibrinolytic therapy or dextran within 2d preceding the first administration of the study drug</p> <p>Intervention 1: Fondaparinux 2.5mg SQ, starting 6± 2h postoperatively, then 12h after first dose, continued q24h for 5-9d post-operative</p> <p>Intervention 2: Enoxaparin 40mg SQ, starting 12 ± 2h preoperatively, then 12-24h after first dose, continued q24h for 5-9d post-operative</p>	<p>Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (11d)</p> <p>Adverse events: Major bleeding, major bleeding leading re-operation, surgical site bleeding (11d)</p>	<p>randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? No</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? No</p> <p>11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Good</p>
Pitto, 2002	<p>Publication type: Full text</p> <p>Geographic location: Germany</p> <p>Funding: Industry</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Computer generated random number sheets</p> <p>Outcome assessment: Duplex images were analyzed by an observer who was blinded</p>	<p>Inclusion criteria: Patients scheduled to have primary THA</p> <p>Exclusion criteria: history or symptoms of deep-vein thrombosis or pulmonary embolism, esophageal disease, or metabolic bone disease or current, ongoing anticoagulation therapy</p> <p>Intervention: Bone vacuum cementing technique</p> <p>Comparator: Standard cementing technique</p>	<p>Duration of followup: 45d</p> <p>Followup: 100% in both arms</p> <p>Final: Fatal PE, nonfatal PE, PE (45d)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (45d)</p> <p>Adverse events: Major bleeding, minor bleeding (45d)</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis</p>

	with regard to the method of fixation of femoral component. Venography results were analyzed by a single experienced radiologist blinded to findings of duplex USS			used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Total number randomized (number randomized in arms of interest): 130 (130)			Overall quality rating: Good
Prandoni, 2002	Publication type: Full text Geographic location: Italy Funding: Unknown Number of centers: 1 Randomization and allocation concealment: Computer generated list was used for randomization Outcome assessment: Information on all suspected (both asymptomatic and symptomatic) outcome events was reviewed and classified by an independent adjudication committee whose members were unaware of the treatment assignment. Total number randomized (number randomized in arms of interest): 360 (360)	Inclusion criteria: Consecutive patients who underwent elective THA and received warfarin prophylaxis during hospitalization; no previous hip surgery on the same side; no history of thromboembolic disorders Exclusion criteria: VTE complications or major bleeding during hospitalization; asymptomatic proximal DVT, as shown by a bilateral CUS examination performed before hospital discharge; need for long-term anticoagulation; unavailability for long-term followup; refusal to give written informed consent. Intervention 1: Warfarin 5mg PO daily starting on second pre-operative day for 28d Intervention 2: Warfarin 5mg PO daily starting on second pre-operative day and continued until hospital discharge	Duration of followup: 90d Followup: 100% in both arms Final: VTE, major VTE, mortality, mortality due to bleeding (90d); fatal PE, nonfatal PE, PE (28d) Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT (60d) Adverse events: Major bleeding (60d)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Can't tell 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
Turpie, 2002	Publication type: Full text	Inclusion criteria ≥18y undergoing a first elective THR or a	Duration of followup: 49d	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline

PENTATH -LON 2000	Geographic location: Canada, USA, Australia	revision of at least one component of a previously implanted total hip prosthesis	Followup: 100% in both arms	characteristics and prognostic factors? Yes
	Funding: Industry	Exclusion criteria: Planned bilateral hip surgery; women of childbearing age if pregnant or not using effective contraception; active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic GI disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery <the previous 3m; planned indwelling, intrathecal, or epidural catheter during the study treatment period; unusual difficulty in achieving epidural or spinal anesthesia; hypersensitivity to heparin, LMWH, porcine products, or iodinated contrast medium; CI to anticoagulant treatment; concomitant intake of any drug that could not be combined with contrast medium; addictive disorders; concentration of SCr > 180 µmol/L in a well hydrated patient; platelet count < 100X10 ⁹ /L; needed anticoagulant treatment or had received any type of anticoagulant, antiplatelet, or fibrinolytic treatment, or dextran within wk preceding the first administration of the study drug	Final: Symptomatic objectively confirmed VTE, fatal PE, nonfatal PE, fatal PE, mortality (49d); mortality due to bleeding (11d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 139			3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: Randomly assigned to 2 treatment groups by a central computer-derived randomization scheme in blocks of four by an independent organization		Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (11d)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Efficacy outcomes, including review of all venograms, bleeding, and death were assessed by a central independent committee, who were unaware of the patients' treatment assignment		Adverse events: Major bleeding, major bleeding leading to re- operation (11d)	5. Were the methods used for randomization adequate? Yes
				6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
	Total number randomized (number randomized in arms of interest): 2275 (2275)	Intervention 1: Fondaparinux 2.5mg SQ QD starting 4-8h post-operative for 5-9d postoperative		Overall quality rating: Good
		Intervention 2: Enoxaparin 30mg SQ BID starting between 12 and 24h post-operative for 5-9d post- operative		
Warwick, 2002	Publication type: Full text	Inclusion criteria: Patients scheduled for unilateral primary TKR	Duration of followup: 90d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: UK	Exclusion criteria:	Followup: Enoxaparin 79.46%	2. Were outcomes assessed using

	<p>Funding: NR</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Random allocation using sealed envelope generated by a computer</p> <p>Outcome assessment: Venograms interpreted by two consultant radiologists with a particular interest in thromboembolism not aware of the outcome of randomization</p> <p>Total number randomized (number randomized in arms of interest): 229 (229)</p>	<p>Refusal of consent; long-term warfarin therapy for pre-existing cardiac or cerebral disease; bleeding tendency; painful joints or wounds in the feet which would preclude the use of the foot pump; participating in an ongoing study of the early discharge of patients after joint arthroplasty</p> <p>Intervention 1: Enoxaparin 40mg SQ q24h starting 12h before surgery and continuing till discharge</p> <p>Intervention 2: VFP (AV Impulse system) applied in the recovery room and used whenever the patient was not bearing weight until discharge</p>	<p>VFP 84.62%</p> <p>Final: Fatal PE, mortality due to bleeding, mortality (post-operative)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: Re-admission (post-operative)</p>	<p>a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? No</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
<p>Barden, 2001</p>	<p>Publication type: Full text</p> <p>Geographic location: Denmark</p> <p>Funding: Unknown</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: NR</p>	<p>Inclusion criteria: Patients undergoing primary THA</p> <p>Exclusion criteria: Marked main trunk and side branch varicosities; fractures; advance arterial diseases; CHF; severe liver disease; paresis or muscle atrophy; patients taking hormonal preparations, ASA, Vit K-antagonists, cytostatic agents.</p> <p>Intervention: Modified position to monitor femoral blood flow</p> <p>Comparator:</p>	<p>Duration of followup: 3 to 3.6 months</p> <p>Followup: 100% in both arms</p> <p>Final: Fatal PE, nonfatal PE, PE (90d)</p> <p>Intermediate: Symptomatic DVT (90d)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Good</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation</p>

	Outcome assessment: NR	Conventional figure of four positioning		concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
	Total number randomized (number randomized in arms of interest): 160 (160)			
Bauer, 2001	Publication type: Full text	Inclusion criteria: ≥ 18y undergoing elective major knee surgery: resection of the distal end of femur or proximal end of tibia or revision of at least one component of a previously implanted total knee prosthesis	Duration of followup: 49d	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: North America		Followup: 100% in all arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry	Exclusion criteria: Surgery in the contralateral knee was performed at the same time or within 2 wks after enrollment; pregnancy or not using active contraception; active bleeding disorder; current ulcerative or angiodysplastic GI disease; hemorrhagic stroke or brain , spinal, ophthalmologic surgery within the previous 3m; insertion of an indwelling intrathecal or epidural catheter during the treatment period; unusual difficulty in administering epidural or spinal anesthesia; hypersensitivity to heparin, LMWH, porcine products or iodinated contrast medium; CI to anticoagulant therapy; current addictive disorder, SCr concentration above 2mg/dL in a well hydrated patient; platelet count below 100,000/cubic mm; requiring anticoagulant	Final: Symptomatic objectively confirmed VTE, fatal PE, nonfatal PE, mortality (49d); PE, mortality due to bleeding (11d)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 64			4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly assigned in a 1:1 ratio in blocks of 4, stratified according to center, through a central computer derived randomization scheme		Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (11d)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: Efficacy and safety outcomes adjudicated by a central independent committee unaware of the treatment assignments		Adverse events: Major bleeding, major bleeding leading to reoperation (11d)	6. Were methods for allocation concealment adequate? Yes
	Total number randomized	Intervention 1: Fondaparinux 2.5mg SQ QD starting 6±2h		7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and

	(number randomized in arms of interest): 1049 (1049)	postoperatively till 5 th to 9 th post-operative d.		insignificant? Yes
Comp, 2001	<p>Publication type: Full text</p> <p>Geographic location: USA</p> <p>Funding: Industry</p> <p>Number of centers: Multicenter</p> <p>Randomization and allocation concealment: Computer-generated randomization scheme stratified by surgical procedure</p> <p>Outcome assessment: A central independent expert panel composed of at least three vascular radiologists blinded to the treatment assignment and outcome interpreted all venograms, ventilation-perfusion lung scans, and pulmonary angiograms made during the double-blind phase. The final diagnosis was assigned by a consensus method. The expert panel did not assess ultrasonograms</p> <p>Total number randomized (number randomized in arms of interest): 873 (873)</p>	<p>Intervention 2: Enoxaparin 30mg SQ BID starting 12-24h postoperatively till 5th to 9th post-operative d</p> <p>Inclusion criteria: Elective primary THR or TKR; written informed consent; received adequate medication during the open label phase of the study; did not require reoperation or have venous thrombosis or major hemorrhage during hospitalization; did not receive excluded concomitant medications</p> <p>Exclusion criteria: Multiple joint replacement or inability to achieve hemostasis <12 -24h after surgery; surgery on the ipsilateral hip/knee < 6m or on the ipsilateral knee/hip, the contralateral knee/hip, or the contralateral hip/knee < 3m; clinical evidence of chronic or acute DVT; hx of VTE<12m before surgery; generalized hemorrhagic diathesis or hypercoagulable syndrome; documented allergy to UFH; hx of heparin-associated thrombocytopenia; skin rash or necrosis; allergy to fish or swine products, iodine, or radiopaque contrast medium; current drug or alcohol abuse; surgery on the eye, spinal cord, or CNS; documented stroke or MI <1m prior to study; active ulcerative disease or GI tract angiodysplasia; active GIB < 6m; uncontrolled HTN; use of aspirin containing products or NSAIDs daily < 4d preceding hospitalization; receipt of another investigational drug < 4w; clinically relevant diseases or treatments that could interfere with study medications or their evaluation</p> <p>Intervention 1: Enoxaparin 30mg SQ BID starting 12-24h post-operative for 7-10d, then 40mg SQ QD for 3w.</p>	<p>Duration of followup: 90d</p> <p>Followup: 100% in both arms</p> <p>Final: VTE, fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (30d)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (30d)</p> <p>Adverse events: Major bleeding (30d), readmission (90d)</p>	<p>Overall quality rating: Good</p> <ol style="list-style-type: none"> 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes <p>Overall quality rating: Good</p>

Intervention 2:
Enoxaparin 30mg SQ BID starting 12-24h post-operative for 7-10d, then placebo injections SQ for 3w

Eriksson, 2001	<p>Publication type: Full text</p> <p>Geographic location: 21 countries</p> <p>Funding: Industry</p> <p>Number of centers: 99</p> <p>Randomization and allocation concealment: Randomly assigned to treatment groups in blocks of 4 with stratification according to center with the use of a computer generated randomization</p> <p>Outcome assessment: Efficacy and safety outcomes were adjudicated by a central independent committee whose members were unaware of the treatment assignments and included review of all venograms and reports of bleeding and death</p> <p>Total number randomized (number randomized in arms of interest):</p>	<p>Inclusion criteria: ≥18y scheduled to undergo standard surgery for fracture of the upper third of the femur, including the femoral head and neck, within 48h after admission</p> <p>Exclusion criteria: Multiple trauma affecting > 1 organ system; interval > 24h between the injury and hospital admission; pregnancy; active bleeding; documented congenital or acquired bleeding disorder; current ulcerative or angiodysplastic GI disease; hx of hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous 3m; planned use of an indwelling intrathecal or epidural catheter for more than 6h after surgery; hypersensitivity to heparin, LMWH, porcine products, or iodinated contrast medium; CI to anticoagulant therapy; current addictive disorder; SCr concentration above 2 mg/dL in a well-hydrated patient; and platelet count < 100,000/cubic mm; required anticoagulant therapy or received dextran or any type of anticoagulant or fibrinolytic therapy from admission to the time of 1st administration of the study drug or surgery</p> <p>Intervention 1: Fondaparinux 2.5mg SQ QD starting 6 6±2h post-operative if surgery was on time (if delayed dose given 12±2h preoperative) for 5-9d post-operative</p> <p>Intervention 2:</p>	<p>Duration of followup: 49d</p> <p>Followup: Fondaparinux 75% Enoxaparin 74%</p> <p>Final: Symptomatic objectively confirmed VTE, fatal PE, nonfatal PE, mortality (49d); mortality due to bleeding (11d)</p> <p>Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (11d)</p> <p>Adverse events: Major bleeding, minor bleeding, major bleeding leading to reoperation (11d)</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? No</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? No</p> <p>11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Fair</p>
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Fitzgerald, 2001	1711 (1711)	Enoxaparin 40mg SQ QD starting 12±2h preoperative for 5-9d post-operative		
	Publication type: Full text	Inclusion criteria: ≥38y; primary unilateral TKA; premenopausal women if surgically sterile or not pregnant	Duration of followup: 21d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: NR	Exclusion criteria: Wound hemorrhage continuing > 8h after wound closure; generalized hemorrhagic disorders or hypercoagulable syndrome, including chronic or acute DVT or hx of VTE; allergy to UFH, warfarin, fish or swine products, iodine, or contrast medium; hx of HIT or heparin or warfarin-associated skin rash or necrosis; asthma not under medical control; surgery on the ipsilateral knee < 6m or on the ipsilateral hip, contralateral hip, or contralateral knee < 3m; clinically important disease or requirement for treatment during the study period that could interfere with study drugs; hepatic disease; renal disease; current abuse of drugs or alcohol; surgery involving the eye, spinal cord, or central nervous system <3m; active ulcerative disease or angiodysplasia of the GI tract or active GI hemorrhage < 6m; HTN not under control; stroke or MI < 3m; treatment with aspirin, aspirin-containing products, or NSAID 4d before hospitalization or regular treatment with these products during hospitalization	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry		Final: PE, mortality due to bleeding, mortality (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: MC		Intermediate: DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Randomization and allocation concealment: Randomization numbers generated by the study sponsor were affixed to the exterior of each sealed medication kit; randomization was performed by the investigator allocating the kits in ascending order		Adverse events: Major bleeding, major bleeding leading to re-operation, minor bleeding, surgical site bleeding, re-operation (post-operative)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: In addition to the assessment by the investigator, a blinded, independent review of all venograms and ultrasonograms was carried out by a panel of vascular imaging specialists			6. Were methods for allocation concealment adequate? Yes
	Total number randomized (number randomized in arms of interest): 349 (349)	Intervention 1: Warfarin 7.5 mg PO starting within 8h after wound closure and dose adjusted to maintain between 2 and 3 for 4-14d postoperatively Intervention 2: Enoxaparin 30mg SQ q12h starting within 8h after wound closure for 4-14d postoperatively		7. Were incomplete outcome data adequately addressed? Yes
Hull, 2000	Publication type: Full text	Inclusion criteria ≥18 y scheduled for elective unilateral THA	Duration of followup: Post-operative	8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair

Kennedy, 2000	Geographic location: USA, Canada	(primary or revision)	Followup: 100% in both arms	factors? Yes
	Funding: Industry, Academia	Exclusion criteria: Documented bleeding <3m before surgery; hypersensitivity to heparin, LMWH, warfarin, or contrast media; defective hemostasis; ongoing anticoagulants; pregnancy or breastfeeding; clinically significant hepatic dysfunction; renal insufficiency; severe HTN; septic endocarditis; < 40 kg; eye, ear, or central nervous system surgery <1m before surgery; diseases with unfavorable prognosis (eg, malignant neoplasms); inability to follow instructions or perform procedures; simultaneous participation in another pharmacological study or use of any investigational drug <30d before surgery; previous randomization into this study; or use of pneumatic compression stockings	Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 29		Intermediate: DVT, symptomatic DVT, proximal DVT (post- operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: Randomized using a computer- derived treatment schedule to assign treatment regimens with the randomization list divided into consecutive blocks to obtain balance of treatments		Adverse events: Major bleeding, minor bleeding, surgical site bleeding (0-1d, 2-8d)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Venograms, lung scan, angiograms interpreted by the local radiologist and an independent, blinded central reader and disagreements resolved by a second blinded independent central interpretation. Two central committee members not involved in the patient's care independently adjudicated the bleeding data using the international classification	Intervention 1: Dalteparin 2500 IU SQ for the 1 st dose followed by 5000 IU QD starting within 2h before surgery Intervention 2: Dalteparin 2500 IU SQ for the 1st dose followed by 5000 IU QD starting within 2h before surgery Intervention 3: Warfarin 10mg PO QD except for ≥70y or <57kg who received 5 mg for the first dose with subsequent doses adjusted to maintain an INR from 2.0 to 3.0 starting postoperatively on the evening of the surgery		5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Total number randomized (number randomized in arms of interest): 1472 (1472)			Overall quality rating: Good
	Publication type: Full text	Inclusion criteria Garden III or IV intracapsular hip fracture; ≤ 60y; direct admission to a hospital	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes

	Geographic location: NR	Exclusion criteria: Previous hx of DVT, PE, CVI or malignant tumor, peptic ulcer disease, gastritis, aspirin sensitivity or who were already on anticoagulation therapy	Followup: Aspirin 91.25% VFP 87.5%	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR		Final: PE (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: NR	Intervention 1: Aspirin 325mg PO BID starting on the day of surgery as soon as the patient was able to tolerate pills orally	Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly allocated by alternate selection to either group	Intervention 2: VFP (AV impulse system) fitted in the recovery room on both feet with the inflatable pad placed under the plantar arch and secured in position for a minimum of 18h/d until the patient was fully ambulatory	Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: Doppler assessment was carried out by staff vascular medicine specialists who were blinded to the prophylactic regimen			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 160 (160)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
Colwell, 1999	Publication type: Full text	Inclusion criteria: ≥ 18y scheduled for elective unilateral primary hip arthroplasty	Duration of followup: 90d	Overall quality rating: Fair
	Geographic location: USA	Exclusion criteria: Hx of blood dyscrasia, HIT; allergy to warfarin or heparin	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry		Final: Symptomatic objectively confirmed VTE, PE, fatal PE, mortality (90d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 156	Intervention 1: Enoxaparin 30mg SQ starting within 24h postoperatively and continuing q12h until discharge (mean of 7.3d)	Intermediate: Symptomatic DVT (90d)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation	Intervention 2:		4. Were outcome assessors blind to exposure/intervention status? Can't tell
				5. Were the methods used for

	<p>concealment: Randomly assigned to treatment groups</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 3011 (3011)</p>	<p>Warfarin 7.5mg PO within 24h post-operative (could be initiated 48h pre-operatively) and continuing with dose adjusted to maintain an INR between 2.0-3.0 until discharge (mean of 7.3d)</p>	<p>Adverse events: Major bleeding, minor bleeding, surgical site bleeding, HIT (post-operative)</p>	<p>randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Levy, 1999	<p>Publication type: Full text</p> <p>Geographic location: Israel</p> <p>Funding: None</p> <p>Number of centers: 3</p> <p>Randomization and allocation concealment: computer generated randomization list</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 58 (58)</p>	<p>Inclusion criteria: Oosteoarthritis of the knee; scheduled to have a unilateral TKA with cement</p> <p>Exclusion criteria: NR</p> <p>Intervention 1: Octacol F15 fibrin tissue adhesive (ten to twenty milliliters of combined product or one or two kits) was then applied by topical spraying with use of a double-syringe spray-device</p> <p>Comparator: No application of octacol F15 fibrin tissue adhesive</p>	<p>Duration of followup: Post-operative</p> <p>Followup: 100% in both arms</p> <p>Final: Fatal PE (post-operative)</p> <p>Intermediate: DVT, symptomatic DVT, asymptomatic DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p>

Planes, 1999	Publication type: Full text	Inclusion criteria: Patients age ≥ 40 y; weight 50kg-90kg scheduled to undergo primary THR	Duration of followup: Post-operative	11. Conflict of interest reported and insignificant? Yes
	Geographic location: France	Exclusion criteria: Allergy to heparin, iodine or radioopaque contrast medium; acquired or hereditary hemostatic disorders; disorders contraindication anticoagulant prophylaxis; severe hepatic or renal failure; severe or malignant HTN; history of DVT or PE within previous 6m; MI or stroke within previous 6m; revision or conversion hip surgery or primary hip arthroplasty of the opposite hip performed <3m previously; advanced cancer; pregnancy	Followup: 100% in both arms	
	Funding: Industry	Intervention 1: Enoxaparin 40mg SQ 12h before surgery, 12h post-surgery and then QD for 15d	Final: Fatal PE, nonfatal PE, mortality, mortality due to bleeding (postoperative)	Overall quality rating: Fair
	Number of centers: 43	Intervention 2: Tinzaparin 4500 antifactor IU Xa SQ 12h before surgery, 12h post-surgery and then QD for 15d	Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (post-operative)	
	Randomization and allocation concealment: Stratification by study center performed by a computer generated randomization schedule balanced in blocks of four		Adverse events: Major Bleeding, minor bleeding, surgical site bleeding, HIT (postoperative)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Outcome assessment: Bleeding and venograms were interpreted locally, then by centralized assessment by an independent expert blind to treatment allocation			
	Total number randomized (number randomized in arms of interest): 499 (499)			Overall quality rating: Good
TIFDED Study Group, 1999	Publication type: Full text	Inclusion criteria: HFS within 24h of fracture and operated on within 48h after hospital entry	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers
	Geographic location: France, Belgium, Norway, Netherlands	Exclusion criteria: <45kg or > 100kg; history of bleeding diathesis; APTT >10% above reference range; uncontrolled HTN; hepatic failure;	Followup: 100% in both arms	
			Final: PE, fatal PE, nonfatal PE	

Wakankar, 1999	Funding: Government/foundation	previous ischaemic or hemorrhagic CVA; fertile women; recent GI bleeding or peptic ulcer; recent use of oral anticoagulants or fibrinolytic drugs; contrast medium, iodine or glycosaminoglycuronan allergy	(post-operative)	blind to the intervention status of participants? No
	Number of centers: 4	Intervention 1: Enoxaparin† A: 20mg SQ 2h before surgery and then 40mg QD about 12h after surgery for 9-11d B: 20mg + 20mg SQ about 2h before surgery and then 40mg QD about 12h after surgery for 9-11d C: 20mg SQ BID the last preoperative dose about 2h before surgery and then 40mg QD about 12h after surgery for 9-11d	Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomly assigned to one of three treatment groups stratified by center		Adverse events: Major bleeding, surgical site bleeding, (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All venograms were coded and independently reviewed by a panel of experts unaware of treatment allocation. All information on patients with hemorrhage was adjudicated by an independent committee	Intervention 2: Dalteparin D: 2500U SQ starting about 2h before surgery then 2500U SQ about 12h after last preoperative dose, then 5000U SQ QD for 9-11d E: 2500U SQ BID the last preoperative dose not within 2h before surgery, 2500U SQ about 12h after last preoperative dose, then 5000U SQ QD for 9-11d		6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 197 (132)			7. Were incomplete outcome data adequately addressed? Yes
Wakankar, 1999	Publication type: Full text	Inclusion criteria Patients undergoing TKA	Duration of followup: 120d	8. Was intention to treat analysis used? Yes
	Geographic location: UK	Exclusion criteria: Diabetes; rheumatoid arthritis; previous thromboembolism; active malignancy; those having one-stage bilateral procedures	Followup: 100% in both arms	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Funding: None		Final: Mortality (120d)	10. Was the overall loss to followup low (< 20%)? Yes
	Number of centers: 1	Intervention 1: TKA under a tourniquet after the leg had been exsanguinated, tourniquet pressure was twice the systolic blood pressure.	Intermediate: DVT, asymptomatic DVT, proximal DVT, distal DVT (post-operative)	11. Conflict of interest reported and insignificant? Yes
	Randomization and allocation concealment:	Comparator:		Overall quality rating: Fair
				1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
				2. Were outcomes assessed using a valid methodology and criteria? Yes
				3. Were subjects and providers blind to the intervention status of participants? No
				4. Were outcome assessors blind to exposure/intervention status? Can't tell
				5. Were the methods used for randomization adequate? No

	Patients randomized into two groups using random numbers	No use of tourniquet	Adverse events: NR	6. Were methods for allocation concealment adequate? No 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Outcome assessment: NR			
	Total number randomized (number randomized in arms of interest): 77 (77)			
Kim, 1998	Publication type: Full text	Inclusion criteria Primary, uncemented THR; ≥18y; obtained informed consent	Duration of followup: Post-operative	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Can't tell
	Geographic location: Korea	Exclusion criteria History of aspirin intolerance; ingested aspirin containing compound or other antiplatelet within 14d prior to surgery	Followup: 100% both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR		Final: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Intervention: EC-aspirin 400mg po TID starting 48h pre-operatively and finishing 14d postoperatively	Intermediate: DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: NR	Comparator: Control	Adverse events: Major bleeding (post-operative)	5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes
	Outcome assessment: NR			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to
	Total number randomized: 150 (100)			

				followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Fair
Lassen, 1998	Publication type: Full text	Inclusion criteria: All patients admitted for THA	Duration of followup: 35d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Denmark	Exclusion criteria: Age < 18y; previous surgery in the study; simultaneous participation in other pharmacological studies; informed consent not obtained; high probability for drop-out; renal insufficiency; hepatic insufficiency and prothrombin < 0.7; platelet count < 100X 10 ⁹ /L; treatment with oral anticoagulants or heparin within 7d before inclusion; hypersensitivity to heparin, LMWH or contrast media; documented bleeding within 3m prior to surgery; intracranial bleeding within 3m prior to surgery; eye, ear, or central nervous system surgery within 1m prior to surgery; hypertension with diastolic pressure >120mmHg; septic endocarditis; body weight <40 kg; known pregnancy or lactation	Followup: 76% overall	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Unknown		Final: NR	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 8		Intermediate: DVT, asymptomatic DVT, proximal DVT (35d)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: NR		Adverse events: Major bleeding, minor bleeding (35d)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All venograms were evaluated by a panel of three radiologists who were unaware of the result of randomization			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 281 (281)	Intervention 1: Dalteparin 5000 antifactor Xa U SQ QD starting 12h before surgery, continuing for 7d post-operative. Same regimen was followed after randomization until 35d post-operative		7. Were incomplete outcome data adequately addressed? Yes
		Intervention 2: Dalteparin 5000 antifactor Xa U SQ QD starting 12h before surgery, continuing for 7d post-operative, then placebo injections (isotonic sodium chloride) QD until 35d post-operative		8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Fair
Rader, 1998	Publication type: Full text	Inclusion criteria: High risk patient undergoing primary THA or TKA; hx of DVT >3y	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location:		Followup:	

Germany	Funding: NR	Exclusion criteria: Proximal fracture of the femur;<18y:long lasting immobilization; decompensated cardiac insufficiency; prolonged arterial sclerosis and occlusion; liver insufficiency; hemorrhagic diathesis; anticoagulation with pheprocoumon; apoplectic insult; pregnancy; tumor history; arthritis and arthrodesis of the lower extremity; manifest PE, DVT, thrombophlebitis; chronic paralysis; chronic muscular atrophies	100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
Number of centers: 1	Randomization and allocation concealment: NR	Intervention 1: Heparin 3 X 5000 IU for 3d, 3 X 7500 IU on 4 th day to maintain a PTT of 40sec	Final: NR	3. Were subjects and providers blind to the intervention status of participants? Can't tell
Outcome assessment: NR	Total number randomized (number randomized in arms of interest): 246 (246)	Intervention 2: Enoxaparin 40mg SQ QD for till hospital discharge (mean of 16.4d)	Intermediate: DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
Adverse events: NR				5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)?Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Ryan, 1998	Publication type: Full text	Inclusion criteria: Patients in whom primary THA has been performed	Duration of followup: Post-operative	Overall quality rating: Fair
Geographic location: USA	Funding: Industry	Exclusion criteria: History of venous thrombi or PE; history of peripheral vascular disease; contraindication to aspirin or magnetic resonance imaging; indwelling vascular stent and/or IVC filter <6w before magnetic resonance venography	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
Number of centers: 1	Randomization and allocation concealment: Randomized to two treatment	Intervention 1: IPC (Venaflow) applied immediately post surgery and worn for first 24h, until patient stood for 1 st time without help of physical	Final: PE, fatal PE, nonfatal PE (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
			Intermediate: Symptomatic DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
			Adverse events:	4. Were outcome assessors blind to exposure/intervention status? Yes
				5. Were the methods used for randomization adequate? Can't tell

	groups	therapy, then continuously for 4 – 5d	NR	6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Outcome assessment: All venography studies were interpreted by one of two senior radiologists blinded to patients treatment allocation Total number randomized (number randomized in arms of interest): 100 (100)	Intervention 2: GCS (T.E.D.) applied immediately post surgery and worn for first 24h, until patient stood for 1 st time without help of physical therapy, then continuously for 4 – 5d		
Warwick, 1998	Publication type: Full text Geographic location: UK Funding: Industry, Government/Foundation Number of centers: 1 Randomization and allocation concealment: Randomization performed with use of sealed envelopes containing a slip indicating the allocation, which had been derived from a computer-generated sequence Outcome assessment: The venogram was interpreted by consensus between two consultant radiologists who had a special interest in	Inclusion criteria: Patients scheduled for primary THR Exclusion criteria: Refusal of consent; long term anticoagulation therapy for preexisting cardiac or cerebrovascular disease; an active malignant tumor; GI ulceration; previous bleeding diatheses; wounds on or painful joints in the feet and enrollment in another trial necessitating planned early discharge from the hospital or modification of wound drainage Intervention 1: Enoxaparin 40mg SQ q24h starting 12h before surgery and continuing till 8 th post-operative d Intervention 2: VFP (AV Impulse system) fitted on both legs in the recovery room and used whenever the patient was not bearing weight until 8 th post-operative d	Duration of followup: 90d Followup: 100% in both arms Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative) Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (post-operative) Adverse events: Discomfort, re-admission (post-operative)	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to exposure/intervention status? Partially 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and

	thromboembolism and were not aware of the randomization category of the patient			insignificant? Yes
	Total number randomized (number randomized in arms of interest): 290 (290)			Overall quality rating: Good
Andersen, 1997	Publication type: Full text	Inclusion criteria: Male or female, age ≥ 18 y; monolateral THR (primary or revision); written informed consent from the patient; ability to continue medications after discharge	Duration of followup: 35d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Denmark		Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government/foundation	Exclusion criteria: Previous participation in the study; participation in other studies that may influence the efficacy and safety of the study; expected low compliance; renal insufficiency measured within the last 3w before inclusion; liver insufficiency measured within the last week before inclusion; impaired hemostasis; treatment with oral anticoagulant heparin or LMWH within days before the inclusion; hypersensitivity to heparin, LMWH, or contrast media; GIB or cerebral bleeding within 3m prior to the inclusion; eye, ear or CNS surgery within 1m prior to the inclusion; HTN with diastolic pressure >120 mm Hg; endocarditis; body weight < 40 kg; known pregnancy or lactation	Final: PE (35d)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: 1		Intermediate: DVT, symptomatic DVT, asymptomatic DVT (35d)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: NR		Adverse events: Reoperation (35d)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: phlebograms were evaluated by three independent radiologists who were unaware of the treatment			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 41 (41)	Intervention 1: Dalteparin 5,000IU SQ QD started the evening before operation, on the operation day, and 2 days after operation and thereafter for 35d		7. Were incomplete outcome data adequately addressed? Yes
		Intervention 2: Dalteparin 5,000IU SQ QD started the evening before operation, on the operation day, and 2 days after operation and thereafter for 5-7d, then placebo injections		8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low ($< 10\%$)? Yes
				10. Was the overall loss to followup low ($< 20\%$)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair

Dahl, 1997	Publication type: Full text	for 28d Inclusion criteria: Consenting male and female patients age >18y admitted for elective primary or secondary arthroplasty of the hip	Duration of followup: 35d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No Overall quality rating: Fair
	Geographic location: Norway Funding: Unknown Number of centers: 2 Randomization and allocation concealment: NR Outcome assessment: venograms were evaluated blindly 6 months later by one specialist. VQ scans and X-rays were evaluated blindly after the study period by a specialist Total number randomized (number randomized in arms of interest): 265 (265)	Exclusion criteria: Known renal of liver insufficiency; cerebral bleeding <3m before surgery or known hemorrhagic diathesis; eye or ear surgery within 1m before surgery; severe hypertension; septic endocarditis; threatened arterial circulation in the leg; a body weight less than 40kg; anticoagulant therapy <1w before surgery; a known hypersensitivity to heparin, LMWH, dextran or contrast media; pregnancy or breastfeeding; inability to comply with the study protocol; previous surgery in the present study Intervention 1: Dalteparin 5000 IU SQ starting evening before surgery and continued daily for 7 days + dextran infusion 500-1000ml on 0d, 1500ml on 1d + below-knee GCS (Kendall) on both legs worn before operation, for first post-operative week. Patients with no DVT or PE during the first post-operative week continued dalteparin 5000 IU SQ daily until 35d Intervention 2: Dalteparin 5000 IU SQ starting evening before surgery and continued daily for 7 days + dextran infusion 500-1000ml on 0d, 1500ml on 1d + below-knee GCS (Kendall) on both legs worn before operation, for first post-operative week. Patients with no DVT or PE during the first post-operative week received placebo injections SQ daily until 35d	Followup: 100% in both arms Final: Fatal PE, nonfatal PE, PE (7-35d) mortality due to bleeding, mortality (35d) Intermediate: DVT (7d, 7-35d, 35d); Symptomatic DVT (7d, 35d); Proximal DVT (35d) Adverse events: NR	
Eriksson, 1997a	Publication type: Full text	Inclusion criteria: ≥18y old, ≥50 kg scheduled to have an	Duration of followup: 42d	1. Were the groups similar at baseline in terms of baseline

Eriksson, 1997b	Geographic location: Sweden, Denmark	elective primary THR	Followup: 100% in both arms	characteristics and prognostic factors? Yes
	Funding: NR	Exclusion criteria: Previous inclusion in the trial; childbearing potential; hemostatic or bleeding disorder; hip fracture or operation < 3m; major operation < last m; cerebral ischemic attack <last 6m; uncontrolled HTN; renal impairment; known allergy to hirudin, heparin, or contrast media	Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding; mortality (42d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 11		Intermediate: DVT (post-operative, post-operative-42d); proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: Computer generated randomization scheme providing balanced blocks of patient numbers for each of the 2 treatment groups within each center, using a block size of 6	Intervention 1: Desirudin 15mg SQ BID starting 30mins before surgery after induction of anesthesia for 8-11d postoperatively	Adverse events: Major bleeding leading to re-operation (42d)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Outcome assessment: All venograms were centrally assessed by 2 independent expert radiologists who were unaware of the results recorded at the local centers	Intervention 2: UFH 5000 IU SQ TID starting 2h before surgery for 8-11d postoperatively		5. Were the methods used for randomization adequate? Yes
	Total number randomized (number randomized in arms of interest): 445 (445)			6. Were methods for allocation concealment adequate? Yes
	Publication type: Full text	Inclusion criteria: ≥18 y, ≥50 kg scheduled to undergo elective primary THR	Duration of followup: 42d	7. Were incomplete outcome data adequately addressed? Yes
	Geographic location: Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland	Exclusion criteria: Childbearing potential; previous inclusion in the trial; bilateral hip operation; hip surgery or fracture of the leg < previous 3m; other major surgery < past m; hemostatic or bleeding disorders; hx of hemorrhagic stroke, intracranial or intraocular bleeding, or	Followup: Desirudin 77% Enoxaparin 76%	8. Was intention to treat analysis used? Yes
	Funding:		Final: Major VTE (post-operative study period); PE (post-	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Good
				1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
				2. Were outcomes assessed using a valid methodology and criteria? Yes
				3. Were subjects and providers blind to the intervention status of participants? Yes

Francis, 1997	Industry	cerebral ischemic attacks < past 6m; GI or pulmonary bleeding < 3m; uncontrolled HTN; renal impairment, nephrectomy, or kidney transplantation; and known allergy to hirudin, heparin, or contrast medium	operative study period, after study period-42d); fatal PE (after study period-42d); mortality (42d)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Number of centers: 31			5. Were the methods used for randomization adequate? Can't tell
	Randomization and allocation concealment: Randomized in a double-blind manner to 2 treatment groups	Intervention 1: Desirudin 15mg BID starting within 30mins before surgery but after induction of regional block anesthesia for 8-12d postoperatively	Intermediate: DVT (post-operative study period, study period-42d); proximal DVT (post-operative study period)	6. Were methods for allocation concealment adequate? Can't tell
	Outcome assessment: All venograms were assessed in a central radiology department by consensus of two radiologists who were unaware of the results recorded at the local centers. An independent safety committee monitored reported adverse events, bleeding complications, laboratory abnormalities, and episodes of DVT as assessed locally	Intervention 2: Enoxaparin 40mg SQ QD starting on the evening before surgery for 8-12d postoperatively	Adverse events: Major bleeding (post-operative study period)	7. Were incomplete outcome data adequately addressed? Yes
	Total number randomized (number randomized in arms of interest): 2079 (2079)			8. Was intention to treat analysis used? No
	Publication type: Full text	Inclusion criteria 18y ≤ scheduled to have a unilateral primary or revision THA	Duration of followup: Post-operative	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Geographic location: USA	Exclusion criteria: SCr level of ≥1.7 mg/dl; defective hemostasis; documented GI or other bleeding <3m before the operation; cerebral hemorrhage <3m before the operation; operative procedure involving the eye, ear, or central nervous system <1m before the operation; a known hypersensitivity to heparin; severe HTN; and a weight < 41 kg; women who were pregnant or breastfeeding,	Followup: 100% in both arms	10. Was the overall loss to followup low (< 20%)? No
	Funding: NR		Final: NR	11. Conflict of interest reported and insignificant? Yes
	Number of centers: 2		Intermediate: DVT, proximal DVT, distal DVT (post-operative)	Overall quality rating: Fair

Nilsson, 1997	Randomization and allocation concealment: Randomly assigned to either of the two treatment groups	those who had reproductive potential unless they had had a negative pregnancy test	Adverse events: Major bleeding, minor bleeding, major bleeding leading to re-operation, surgical site bleeding, bleeding leading to transfusion, re-operation (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All venograms were evaluated by a radiologist who had no knowledge of the treatment group assignment. All lung scans and pulmonary angiograms were reviewed by an independent third-party evaluator who did not have knowledge of the treatment-group assignment	Intervention 1: Dalteparin SQ 2500 IU for the first 2 doses, 5000 IU QD on following post-operative days starting within 2h before surgery, continued until venography Intervention 2: Warfarin PO QD 5mg for $\leq 57\text{kg}$, 7.5mg for $>57\text{kg}$ for the first 2 doses with subsequent doses adjusted to maintain INR of 2.5 starting evening before surgery, continued until venography		6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low ($< 10\%$)? Yes 10. Was the overall loss to followup low ($< 20\%$)? Yes 11. Conflict of interest reported and insignificant? No
Nilsson, 1997	Total number randomized (number randomized in arms of interest): 580 (580)			Overall quality rating: Fair
	Publication type: Full text Geographic location: Sweden Funding: Unknown Number of centers: 1 Randomization and allocation concealment: NR Outcome assessment: Each phlebogram was examined by a committee of three radiologists unaware of patients' group assignment. All interpretations and	Inclusion criteria: Patients undergoing primary elective hip arthroplasty Exclusion criteria: Renal insufficiency; hypersensitivity to contrast medium, heparin, or LMWH; a past or present risk of hemorrhage; endocarditis, severe liver disease, or untreated hypertension; VTE within the preceding three months; if they had received treatment with heparin, LMWH, oral anticoagulants, or NSAIDs within 5d before surgery; ipsilateral hip surgery within the preceding 6m; pregnant or lactating; lack of informed consent Intervention 1: Enoxaparin 40mg SQ QD starting 12h before surgery, then continued for $30 \pm 4\text{d}$ Intervention 2:	Duration of followup: 90d Followup: 100% in both arms Final: VTE, fatal PE, nonfatal PE, PE (30d); mortality due to bleeding, mortality (90d) Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (30d) Adverse events: NR	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to

	<p>classifications were made before the randomization code was broken</p> <p>Total number randomized (number randomized in arms of interest): 262 (262)</p> <p>Publication type: Full text</p> <p>Geographic location: France</p> <p>Funding: Industry</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomization was balanced in blocks of four by a computer-generated randomization schedule.</p> <p>Outcome assessment: During the study period, patients were assessed by their attending physician, private nurses, or the medical staff of the convalescent homes who were all aware of the study protocol. The double blind for patient nurses, attending nursing and investigators was maintained until database was closed</p> <p>Total number randomized (number randomized in arms of interest): 179 (179)</p>	<p>Enoxaparin 40mg SQ QD starting 12h before surgery for 9 ±2d, then placebo for 21d</p> <p>Inclusion criteria: Consecutive hospital inpatients; > 45y; 45–95 kg; undergone primary THR or conversion or revision THR surgery; receiving LMWH prophylaxis for postoperative VTE; able to walk with crutches without assistance; did not have a diagnosis of DVT, as assessed by bilateral ascending contrast venography of the legs no more than 5d before discharge; availability for a followup assessment 21 days after discharge</p> <p>Exclusion criteria: History of documented DVT or PE in the previous 6m; active cancer; underlying bleeding disorders or hemostatic abnormalities; active gastroduodenal ulcer; a history of hypersensitivity to heparin or to radiopaque media; renal or hepatic insufficiency; uncontrolled hypertension; and recent stroke < 6m</p> <p>Intervention 1: Enoxaparin 40mg SQ QD starting immediately before surgery until just before hospital discharge, then continued for 21d postdischarge.</p> <p>Intervention 2: Enoxaparin 40mg SQ QD starting immediately before surgery until just before hospital discharge, then placebo injections for 21d postdischarge</p>	<p>Duration of followup: 90d</p> <p>Followup: Extended prophylaxis: 94.44% Control: 98.88%</p> <p>Final: fatal PE, nonfatal PE, PE (35d); mortality due to bleeding, mortality (35d, 90d)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (35d)</p> <p>Adverse events: Major bleeding, minor bleeding, bleeding leading to transfusion (35d)</p>	<p>followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No</p> <p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Good</p>
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Samama, 1997	Publication type: Full text	Inclusion criteria: > 18 y; 45–95 kg; primary THR under regional anesthesia (subarachnoid block and catheter removed at the end of the surgical procedure); wearing GCS (started day before surgery)	Duration of followup: 10±2d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Yes 4. Were outcome assessors blind to exposure / intervention status? Partially 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (<10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No Overall quality rating: Good
	Geographic location: France	Exclusion criteria: Re-operation for THR; surgery under general anesthesia; nail extension before surgery; history of DVT, PE, or both; hepatic or renal insufficiency; lung or heart failure; anesthesia status >3, hemorrhagic disorders CI use of antithrombotic drugs (active ulcerative disease, uncontrolled arterial HTN, stroke within previous 6m or other known hemorrhagic disorders), occurrence of a bloody tap during spinal puncture; platelet <100 X 10 ⁹ /L; history of HIT; allergic reaction to heparin, LMWH, or contrast dye; female of childbearing potential; heparin >24h before surgery; oral anticoagulant within 3d; antiplatelet drug for >8d; NSAID within 2d	Followup: Enoxaparin 91.8%, placebo 88.2%	
	Funding: NR		Final: PE, Fatal PE, non-fatal PE, mortality, mortality due to bleeding (10±2d)	
	Number of centers: 11		Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (10±2d)	
	Randomization and allocation concealment: Computer-generated randomization schedule, which was equilibrated by study center and balanced in blocks of 4 patients		Adverse events: Major bleeding, minor bleeding (post-operative)	
	Outcome assessment: Independent central reading committee for venographies, angiographies or lung scans, and if necessary 3 rd party from data and safety monitoring review board; all venograms were evaluated by 2 independent radiologists unaware of the treatment	Intervention: Enoxaparin 40mg SQ daily for 10 ± 2d Comparator: Placebo (SQ saline injections)		
	Total number randomized: 170 (170)			
Eriksson, 1996	Publication type: Full text	Inclusion criteria: Patients scheduled to undergo elective primary THR	Duration of followup: 42d	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers
	Geographic location: Europe	Exclusion criteria: < 21 y; ≤50 kg; recent trauma, bleeding or surgery; bleeding diatheses; renal impairment; childbearing potential; previous	Followup: 100% in both arms	
	Funding:		Final:	

	NR	inclusion in the trial; known allergy to hirudin, heparins or radiopaque contrast media	Fatal PE, nonfatal PE, PE, mortality due to bleeding (post-operative); mortality (42d)	blind to the intervention status of participants? Yes
	Number of centers: 17	Intervention 1: Desirudin 15mg BID starting before surgery after induction of regional block anesthesia for 8-11d postoperatively	Intermediate: DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Randomization and allocation concealment: Randomized in equal numbers within each center	Intervention 2: UFH 5000 IU SQ TID starting 2h before surgery for 8-11d postoperatively	Adverse events: Major bleeding leading to re-operation, surgical site bleeding (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All venograms were centrally assessed by two independent expert radiologists who were unaware of the recorded results at the local center			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 1119 (554)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
Kalodiki, 1996	Publication type: Full text	Inclusion criteria: >40y, unilateral THR for the first time (with or without cement) under GA	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: NR	Exclusion criteria: Established documented coagulation tests+APTT including platelet counts <100 X 10 ⁹ /L; acute bleeding and/or recently documented hemorrhage and any other bleeding risk; anticoagulant therapy 14d before surgery or during study; aspirin 5d or NSAIDs 2d before surgery; severe arterial HTN, history of stroke or neurosurgery in previous 6m; endocarditis; ARF, CRF, severe hepatic or pancreatic disease; hypersensitivity to heparin or metabisulphite; allergy to porcine derived products, iodine or radio-opaque contrast media; history of HIT; previous surgery of the ipsilateral hip;	Followup: Total 100%	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry		Final: NR	2. Were outcomes assessed using a valid methodology and criteria?
	Number of centers: 1		Intermediate: DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Partially
	Randomization and allocation concealment: Patients given consecutive numbers with correspondingly-numbered boxes which contained prefilled syringes of		Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Yes
				5. Were the methods used for randomization adequate? Yes
				6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes

Laupacis, 1996	placebo or enoxaparin and instructions whether GCS should be added; randomization performed by opening consecutively-numbered sealed envelopes	surgery carried out under regional anesthesia; clinical signs of DVT and/or history of recent DVT and/or PE; presence of malignant growths; mental disorders and/or failure to give informed consent		8. Was intention to treat analysis used? No
	Outcome assessment: Venograms and perfusion lung scans were reported on by a consultant radiologist who was not aware of the form of prophylaxis, venography results, or V/Q scan results	Intervention 1: Thigh-length GCS (TEDR) applied preoperatively bilaterally until discharge + enoxaparin 40mg SQ 12h preoperatively then QD until discharge		9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Total number randomized: 78 (78)	Intervention 2: Enoxaparin 40mg SQ 12h preoperatively then QD until discharge		10. Was the overall loss to followup low (< 20%)? Yes
	Publication type: Full text	Comparator: Placebo (SQ injections)	Duration of followup: Post-operative	11. Conflict of interest reported and insignificant? No
	Geographic location: Canada	Inclusion criteria: Patients undergoing unilateral, elective hip arthroplasty for osteoarthritis	Followup: 100% in both arms	Overall quality rating: Good
	Funding: Government/foundation	Exclusion criteria: NR	Final: PE (post-operative)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Number of centers: 1	Intervention 1: Cemented Mallory head prostehsis	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Randomization and allocation concealment: Stratification by age and surgeon	Comparator: Uncemented Mallory head prosthesis	Adverse events: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Outcome assessment: Venograms were read by one of two radiologists			4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Total number randomized (number randomized in arms of interest): 250 (250)			5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes

Leclerc, 1996	Publication type: Full text	Inclusion criteria: Adult patients having knee arthroplasty	Duration of followup: 180d	11. Conflict of interest reported and insignificant? Yes
	Geographic location: Canada	Exclusion criteria: Allergy to contrast material; need for oral anticoagulant or antiplatelet agents; bleeding diathesis; GI hemorrhage < 3m of surgery; renal or hepatic insufficiency; uncontrolled HTN; illicit drug use or alcohol abuse; participation in the present study < last 3m; hemorrhagic stroke < 3m of surgery; receipt of other investigational drugs in the past m; warfarin allergy	Followup: 100% in both arms	Overall quality rating: Fair
	Funding: Industry		Final: Symptomatic objectively confirmed VTE, mortality (180d); nonfatal PE, fatal PE, PE (post-operative)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Number of centers: 8			2. Were outcomes assessed using a valid methodology and criteria? Yes
	Randomization and allocation concealment: Randomized in a 1:1 blocks of four by a computer generated randomization list stratified by study center, hx of VTE, and use of a cemented or uncemented prosthesis.	Intervention 1: Enoxaparin 30mg SQ, starting morning of first day after surgery, continued q12h for 14d or until hospital discharge whichever occurred first	Intermediate: DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Outcome assessment: All diagnostic tests and bleeding episodes were adjudicated by a central committee that was unaware of treatment allocation or clinical findings	Intervention 2: Adjusted dose warfarin to maintain an INR between 2.0 and 3.0 starting evening of day of surgery, continued QD for 14d or until hospital discharge whichever occurred first	Adverse events: Major bleeding, minor bleeding (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Total number randomized (number randomized in arms of interest): 670 (670)			5. Were the methods used for randomization adequate? Yes
Lotke, 1996	Publication type: Full text	Inclusion criteria: Consecutive patients having primary or revision THA or TKA	Duration of followup: Post-operative	6. Were methods for allocation concealment adequate? Yes
	Geographic location:		Followup:	7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Good
				1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes

USA		Exclusion criteria: < 45y; refused consent; administrative omission in enrollment; allergy to contrast dye; either a postoperative VQ scan or postoperative venogram was not obtained	80.4% overall	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government/foundation		Final: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: NR	Intervention 1: Aspirin 325 mg PO BID starting on the day of admission and continued for 6wks post-operative	Intermediate: DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: NR		Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: The VQ scans and venograms were interpreted without knowledge of prophylactic Regimen	Intervention 2: Warfarin 10mg PO on the night of surgery, none the next day, and QD for 6wks to maintain PT between 1.2 and 1.5 X control value		6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 388 (388)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Schwartzmann, 1996	Publication type: Full text	Inclusion criteria: Elective primary THA; > 50 kg; > 40y	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: Brazil	Exclusion criteria: Coagulation disorders; hx of purpura or TCP; recent acute bleeding or bleeding risks; use of clotting or antiplatelet agents < 2 wks before surgery; moderate HTN; inflammatory disease; stroke; systemic infection or endocarditis; organ, kidney, liver or pancreatic insufficiency; hypersensitivity to heparin or LMWH; allergy to fish and swine products; allergy to iodine or radiological contrast media; previous episode of DVT or PE; previous THA; pregnancy or lactation;	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: NR		Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: NR			3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation		Intermediate: DVT, asymptomatic DVT< symptomatic DVT, proximal	4. Were outcome assessors blind to exposure/intervention status? Can't tell
				5. Were the methods used for

	concealment: Randomized to either treatment groups	cancer; use of corticoids or estrogen; mental disorders	DVT, distal DVT(post-operative)	randomization adequate? Can't tell
	Outcome assessment: NR	Intervention 1: Enoxaparin 40mg SQ QD starting immediately post-operative for a duration of 10d post-operative	Adverse events: NR	6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 99 (99)	Intervention 2: UFH 5000 IU SQ q8h starting immediately post-operative for a duration of 10d post-operative		7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
Stannard, 1996	Publication type: Full text	Inclusion criteria: Patients undergoing elective uncemented THA for underlying hip arthrosis	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: USA	Exclusion criteria: Patients with prior history of DVT or PE; femoral neck fracture; age<18y; preexisting extremity vascular disease	Followup: 100% in all arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: NR		Final: Mortality, mortality due to bleeding (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Intervention 1: UFH 5000U SQ daily X3d then EC-aspirin 325mg po BID	Intermediate: DVT, symptomatic DVT, asymptomatic DVT, proximal DVT, distal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: NR	Intervention 2: VFP (PlexiPulse) applied immediately after surgery bilaterally for 16h/d for first 3d and then 12h/d for the remainder of the study	Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Surgeons and radiologists were blinded regarding the patient treatment groups	Intervention 3: UFH 5000U SQ daily X3d then EC-aspirin 325mg po BID plus VFP (PlexiPulse) applied immediately after surgery bilaterally for 16h/d		5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes

	Total number randomized (number randomized in arms of interest): 75 (75)	for first 3d and then 12h/d for the remainder of the study		10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
Stone, 1996	<p>Publication type: Full text</p> <p>Geographic location: UK</p> <p>Funding: NR</p> <p>Number of centers: NR</p> <p>Randomization and allocation concealment: Randomized to 2 treatment groups</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 50 (50)</p>	<p>Inclusion criteria Primary THR</p> <p>Exclusion criteria Antiplatelet therapy; known cancer; thromboembolism/PE; GI or ulcer in past year; social circumstances; complex medical problems; human error</p> <p>Intervention 1: IPC (Flowtron DVT garment) applied to the opposite limb during surgery and to the operated limb after the procedure, continuing until discharge or until 10d postoperatively</p> <p>Intervention 2: Enoxaparin 40mg SQ QD starting on the evening before surgery, continuing until discharge or 10d postoperatively</p>	<p>Duration of followup: Post-operative</p> <p>Followup: 100% in both arms</p> <p>Final: NR</p> <p>Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Good</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? No</p>
Westrich, 1996	<p>Publication type: Full text</p>	<p>Inclusion criteria: Primary unilateral or a one-stage bilateral TKA</p>	<p>Duration of followup: Post-operative</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Partially</p>

Williams-Russo, 1996	Geographic location: USA	Exclusion criteria: History of DVT, PE, peptic ulcer disease or allergy to aspirin; current anticoagulation therapy	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Unfunded		Final: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Intervention: Aspirin 325mg PO BID starting post operatively on the night of the surgery for the study duration + VFP (PlexiPulse) applied in the recovery room and used while the patient was recumbent and removed only for walking and daily hygiene until venogram screening	Intermediate: DVT, proximal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Randomized using a computer generated randomization table	Comparator: Aspirin 325mg PO BID starting post operatively on the night of the surgery for the study duration	Adverse events: Major bleeding, minor bleeding (post-operative)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: Radiologist who read the venogram and ultrasound was blinded to the study group			6. Were methods for allocation concealment adequate? Yes
	Total number randomized: 122 (122)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
	Publication type: Full text	Inclusion criteria: Patients undergoing elective primary unilateral TKR with participating orthopedic surgeons	Duration of followup: 180d	Overall quality rating: Good
	Geographic location: USA	Exclusion criteria: Age \leq 40y; history of surgery performed with either a regional or general anesthetic in the 3m preceding TKR; presence of a contraindication to either epidural anesthesia or general anesthesia	Followup: 94.7% overall	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Government/Foundation		Final: Mortality (180d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Intervention 1: General anesthesia: Induction: thiopental sodium, fentanyl, and vecuronium;	Intermediate: DVT, proximal DVT, distal DVT (180d)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation			4. Were outcome assessors blind to exposure/intervention status? Yes
				5. Were the methods used for

	<p>concealment: Randomized by a blocked schedule based on random numbers table</p> <p>Outcome assessment: Radiologist reading venograms and lung scan were blind to anesthesia status</p> <p>Total number randomized (number randomized in arms of interest): 262 (262)</p>	<p>maintenance: fentanyl, inhaled nitrous oxide (70%), and isoflurane; neuromuscular blockade was reversed with neostigmine and atropine or glycopyrrolate</p> <p>Intervention 2: Epidural anesthesia: Either lidocaine 2% or bupivacaine 0.75%, adjunctive medications for sedation included midazolam and fentanyl</p>	<p>Adverse events: NR</p>	<p>randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Abdel-Salam, 1995	<p>Publication type: Full text</p> <p>Geographic location: England</p> <p>Funding: Unknown</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Patients were allocated to one of two groups using a card system</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 80 (80)</p>	<p>Inclusion criteria: TKR patients; non-diabetic patients who had no previous knee surgery and who had a normal neurovascular supply to the leg (proved by Doppler studies)</p> <p>Exclusion criteria: NR</p> <p>Intervention1: A pneumatic tourniquet placed around the thigh and inflated. The limb was first exsanguinated by elevation for two minutes and the tourniquet was inflated to twice the systolic blood pressure</p> <p>Comparator: A pneumatic tourniquet placed around the thigh but not inflated.</p>	<p>Duration of followup: 730d</p> <p>Followup: 100% in all arms</p> <p>Final: NR</p> <p>Intermediate: DVT, proximal DVT, distal DVT (730d)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Good</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? No</p> <p>6. Were methods for allocation concealment adequate? No</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p>

				<p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Avikainen, 1995	<p>Publication type: Full text</p> <p>Geographic location: Finland</p> <p>Funding: NR</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomized to receive either of the two treatment arms in an unblinded fashion</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 167(167)</p>	<p>Inclusion criteria: Elective hip replacement; informed consent</p> <p>Exclusion criteria: Regular anticoagulant and/or antiplatelet (<14d before surgery); bleeding disorder; platelet (<100*109/l); acute or recent bleeding (<6wks); severe arterial HTN; hx of stroke during past 6m or paralysis of the lower limbs; endocarditis lenta; clinical signs of actual or hx of recent DVT (<3m); SCr>150μmol/l; severe hepatic and pancreatic disease; hypersensitivity to heparin; pregnancy and lactation; mental disorder and failure to give informed consent</p> <p>Intervention1: Enoxaparin 40mg/ 0.4ml SQ starting 12h before surgery and continued BID for 10d postoperatively</p> <p>Intervention2: UFH 500 IU SQ starting 2h before surgery and BID for 10d postoperatively</p>	<p>Duration of followup: Post-operative</p> <p>Followup: 100% in both arms</p> <p>Final: PE (post-operative)</p> <p>Intermediate: DVT, symptomatic DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? No</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant Yes</p>
Colwell, 1995	<p>Publication type: Full text</p> <p>Geographic location:</p>	<p>Inclusion criteria: Male, premenopausal female(if documented to be not pregnant) or postmenopausal female patients 40y of age or older for</p>	<p>Duration of followup: 21d after last medication dose</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p>

USA		elective TKA		
	Funding: NR	Exclusion criteria: Failure to achieve post-operative hemostasis; documented hx of positive clinical evidence of DVT; hx of generalized hemorrhagic disorders or any clinically significant diseases that might interfere with study medications; documented allergy to UFH, fish, swine products or radioopaque dye; uncontrolled asthma; hx of heparin associated TCP or skin rash; current evidence of drug or alcohol abuse; active ulcerative disease or GI hemorrhage within past 6m; uncontrolled HTN; surgery on the eye, spinal cord, or central nervous system within 3m; scheduled simultaneous multiple joint replacements; documented CVA within last 3m; treatment with aspirin or NSAID on a regular basis for 4d preceding hospitalization; pregnancy	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 25		Final: PE, fatal PE, nonfatal PE (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: Randomized to treatment groups		Intermediate: DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Venograms and ultrasonograms read in a blinded manner by an institutionally qualified radiologist, physician or imaging specialist other than the principal investigator at each study site. Ultrasonogram videocassette recordings or hard copy format showing DVT were sent 2 experts for independent review. VQ scans and pulmonary angiogram assessments interpreted by qualified radiologist or physician other than principal investigator blinded to treatment regimens	Intervention 1: Enoxaparin 30mg SQ q12h starting within 8h post-operative for 7d	Adverse events: Major bleeding, minor bleeding, surgical site bleeding (post-operative)	5. Were the methods used for randomization adequate? Can't tell
		Intervention 2: Heparin 5000 U SQ q8h starting within 8h post-operative for 7.1d		6. Were methods for allocation concealment adequate? Can't tell
Warwick, 1995	Total number randomized (number randomized in arms of interest): 453 (453)			7. Were incomplete outcome data adequately addressed? Yes
	Publication type: Full text	Inclusion criteria Primary THR	Duration of followup: Post-operative	8. Was intention to treat analysis used? Yes
	Geographic location: UK	Exclusion criteria Recent aspirin consumption; medical requirement for continued NSAID intake; history of previous VTE	Followup: 100% in both arms	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Funding:		Final:	10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair
				1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
				2. Were outcomes assessed using a valid methodology and criteria? Yes
				3. Were subjects and providers

	Government/foundation; academia	Intervention: Enoxaparin 40mg SQ 12h pre-operatively, 12h and 36h for 3d.	PE (post-operative)	blind to the intervention status of participants? No
	Number of centers: 1	Comparator: Control	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: NR		Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: Venograms were interpreted by consensus of 2 consultant radiologists unaware of randomization			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized: 156 (156)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Colwell, 1994	Publication type: Full text	Inclusion criteria: ≥40y scheduled for primary or revision hip replacement surgery	Duration of followup: 42d	Overall quality rating: Good
	Geographic location: USA	Exclusion criteria: Operation on ipsilateral leg within previous 3m; hx of documented DVT or PE; heparin associated TCP; bleeding disorders; operation on the eye, spinal cord, nervous system within previous 3m; active ulcerative disease of the alimentary tract; uncontrolled HTN; use of NSAID during 4d before operation	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry		Final: PE, nonfatal PE (post- operative, discharge -42d) fatal PE, mortality (post- operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 34			3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment Randomly assigned to one of the 3 different treatment groups in a 1:1:1 ratio using a computer	Intervention 1: Enoxaparin 30mg SQ q12h starting within 24h postoperatively and continued for 7d	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
			Adverse events: Major bleeding, minor	5. Were the methods used for randomization adequate? Yes
				6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data

	generated randomization schedule	Intervention 2: Enoxaparin 40mg SQ QD starting within 24h postoperatively and continued for 7d	bleeding, surgical site bleeding, HIT(post-operative); readmission (discharge-42d)	adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Outcome assessment: NR	Intervention 3: UFH 5000 U SQ q8h starting within 24h postoperatively and continued for 7d		
	Total number randomized (number randomized in arms of interest): 610 (610)			
Fauno, 1994	Publication type: Full text	Inclusion criteria >40y, scheduled to have primary unilateral TKR and diagnosed as having osteoarthritis or rheumatoid arthritis	Duration of followup: 60d	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Finland, Denmark		Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry	Exclusion criteria Use of anticoagulant, platelet aggregation inhibitors, salicylates or NSAID within 7d before the operation; hx of bleeding disorder; abnormal preoperative coagulation values, including platelet count < 80 X 10 ⁹ /l or a PT outside range of 80-10 % of normal, indications of internal bleeding ; untreated HTN; hypersensitivity to heparin or contrast media; previous DVT or PE	Final: Fatal PE, nonfatal PE, PE (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Partially
	Number of centers: 3		Intermediate: DVT, proximal DVT (post-operative); symptomatic DVT (post-operative-60d)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Randomization and allocation concealment: Randomized using sealed envelope			5. Were the methods used for randomization adequate? Yes
	Outcome assessment: All venograms examined independently by 3 radiologists who were unaware of the assigned drug	Intervention 1: Enoxaparin 40mg SQ QD starting on the evening before surgery for 7-10d postoperatively	Adverse events: NR	6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes
	Total number randomized (number randomized in arms of interest): 185 (185)	Intervention 2: UFH 5000 IU SQ TID starting evening before surgery for 7-10d postoperatively		9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes

Lieberman , 1994	Publication type: Full text	Inclusion criteria: Patients >39y; primary unilateral or bilateral hip arthroplasty under hypotensive epidural anesthesia	Duration of followup: 90d	Overall quality rating: Good 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
	Geographic location: USA	Exclusion criteria: Previous VTE; allergy to aspirin or iodinated contrast medium; peptic ulcer disease; venous stasis ulcers of the lower extremity; hypercoagulable state or bleeding dyscrasia; CI to hypotensive epidural anesthesia	Followup: 100% in both arms	
	Funding: Unfunded	Intervention: EC-aspirin 325 mg PO BID starting on the day of the operation for 3w+ IPC (Kendall SCD, thigh high) applied in the recovery room on the day of operation and worn continuously except when bathing or walking until venogram on postoperative day 6-8	Final: PE, fatal PE, nonfatal PE (90d); mortality, mortality due to bleeding (post-operative)	
	Number of centers: 1	Comparator: EC-aspirin 325 mg PO BID starting on the day of the operation for 3w	Intermediate: Proximal DVT, distal DVT (post-operative)	
	Randomization and allocation concealment: Randomized to one of the 2 groups with the use of a random numbers table		Adverse events: NR	
	Outcome assessment: All venograms were analyzed in a blinded fashion by 1 radiologist			
	Total number randomized (number randomized in arms of interest): 231 (231)			
Menzin, 1994	Publication type: Full text	Inclusion criteria: Age ≥ 37 undergoing elective hip replacement	Duration of followup: Post-operative	Overall quality rating: Good 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers
	Geographic location: USA	Exclusion criteria: Ipsilateral hip surgery in prior 3 months; history of VTE; bleeding disorders or HIT; known allergy to UFH	Followup: 99.34% overall	
	Funding:		Final:	

	Industry		NR	blind to the intervention status of participants? No
	Number of centers: 32	Intervention 1: Enoxaparin 30mg SQ q12h, starting within 24h after surgery for at least 7d	Intermediate: DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: NR	Intervention 2: Enoxaparin 40mg SQ QD, starting within 24h of surgery, then continued for at least 7d	Adverse events: Major bleeding (postoperative)	5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell
	Outcome assessment: NR	Intervention 3: UFH 5000U SQ q8h, starting within 24h of surgery, then continued for at least 7d		7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes
	Total number randomized (number randomized in arms of interest): 607 (607)			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
Santori, 1994	Publication type: Full text	Inclusion criteria: Patients undergoing primary THR under general anesthesia by a direct lateral approach	Duration of followup: 42d	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Italy		Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR	Exclusion criteria: Previous hx of thromboembolism, varicose veins, venous insufficiency in the legs, or the presence of a malignant neoplasm	Final: Mortality due to bleeding, mortality (42d)	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: NR	Intervention 1: Heparin 5000 IU SQ TID starting the day before surgery for a duration of 10d	Intermediate: DVT (42d)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: Randomized by a casual numbers table, using sequentially numbered, sealed	Intervention 2: VFP (AV impulse system) fitted to both feet immediately after surgery and worn during all times in bed and interrupted only for	Adverse events: NR	5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data

	envelopes	physiotherapy and walking for 7-10d		adequately addressed? Yes
	Outcome assessment: NR			8. Was intention to treat analysis used? Yes
	Total number randomized (number randomized in arms of interest): 132 (132)			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Hull, 1993	Publication type: Full text	Inclusion criteria ≥18y scheduled to undergo THA or TKA	Duration of followup: 90d	Overall quality rating: Fair
	Geographic location: USA, Canada	Exclusion criteria: Currently active bleeding or disorders contraindicating anticoagulant therapy; hx of DVT or PE; allergy to heparin, bisulphites, or fish; allergy to radiopaque contrast medium; documented deficiency of antithrombin III, protein C, or protein S; hx of heparin-associated TCP; pregnancy; severe malignant HTN; severe hepatic failure (hepatic encephalopathy); severe renal failure necessitating dialysis; or geographic inaccessibility preventing them from making followup visits	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Industry, Government/foundation		Final: Symptomatic objectively confirmed VTE, fatal PE, nonfatal PE (discharge - 90d), mortality due to bleeding, mortality (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 4		Intermediate: DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Randomization and allocation concealment: Randomized using a computer-derived treatment schedule balanced in blocks of 4, stratified into groups according to the study center	Intervention 1: Tinzaparin 75 IU/kg SQ QD starting 18-24h after surgery and continued until 14 th postoperatively, venography or until discharge	Adverse events: Major bleeding, minor bleeding, surgical site bleeding (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Data on the outcome measures of effectiveness (venous thrombosis) and safety (bleeding complications) and on patients' deaths were interpreted by a central adjudicating committee. Two committee members not	Intervention 2: Warfarin 10mg PO for the 1 st dose with subsequent doses QD adjusted to maintain an INR between 2.0 and 3.0 starting on the evening before surgery and continued until 14 th post-operative day, venography or		5. Were the methods used for randomization adequate? Yes
				6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes

	involved in the patient's care adjudicated, and disagreements were resolved by a third member	discharge		Overall quality rating: Good
	Total number randomized (number randomized in arms of interest): 1436 (1436)			
Fordyce, 1992	Publication type: Full text	Inclusion criteria: Patients with osteoarthritis undergoing primary THR	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: UK	Exclusion criteria: NR	Followup: VFP 92.86%; control 95.24%	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: None from any commercial party	Intervention: VFP (A-V Impulse System) applied postoperatively to the foot of operated limb	Final: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Comparator: Control	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Partially
	Randomization and allocation concealment: Randomly assigned to 1 of the 2 groups by use of cards in sealed envelope		Adverse events: Hemorrhagic complication (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: Venograms independently assessed, blind, by 2 radiologists and vascular surgeon			6. Were methods for allocation concealment adequate? Yes
	Total number randomized: 84 (84)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Good
Francis, 1992	Publication type: Full text	Inclusion criteria Patients scheduled for primary THR	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline

	Geographic location: USA	Exclusion criteria: <18y; revision of a previous hip replacement; allergy to contrast media; receiving aspirin or long term anticoagulant therapy; underlying bleeding from GI or urinary tract	Followup: 86.64% overall	characteristics and prognostic factors? Yes
	Funding: Government/foundation		Final: Mortality due to bleeding, mortality (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 2	Intervention 1: Warfarin PO 2 step regimen with dose adjustments to achieve an INR of 1.5 on the day of surgery and 2.5 postoperatively starting 10-14d pre-operatively, continued until venography	Intermediate: DVT, proximal DVT (post- operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: Randomized using a computer generated randomization scheme	Intervention 2: IPC (Kendall Inc.) applied in the operating room immediately before surgery worn at all times while in bed but removed as needed for nursing care or ambulation, continued until venography	Adverse events: Minor bleeding, major bleeding leading to re- operation, bleeding leading to transfusion (post- operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: Venograms were interpreted by a single radiologist unaware of the treatment group			5. Were the methods used for randomization adequate? Yes
	Total number randomized (number randomized in arms of interest): 232 (232)			6. Were methods for allocation concealment adequate? Yes
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Can't tell
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Jorgensen , 1992	Publication type: Full text	Inclusion criteria: Patients admitted for hip fracture surgery; ≥ 40y	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: Denmark	Exclusion criteria: Bleeding disorders; hepatic or renal insufficiency; previous septic endocarditis; cerebral hemorrhage during the preceding 6m; hypersensitivity to heparin or iodine; anticoagulant therapy within 1w of surgery; patients from nursing homes	Followup: Dalteparin 73.2%; placebo 92.7%	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: NR		Final: Mortality, mortality due to bleeding (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers:			3. Were subjects and providers blind to the intervention status of participants? Yes
				4. Were outcome assessors blind to exposure/intervention status?

1		Intervention: Dalteparin 2500 IU SQ 2h pre-operatively and 12h postoperatively, then 5000 IU daily for 6 days	Intermediate: DVT (post-operative)	Can't tell
Randomization and allocation concealment:			Adverse events:	5. Were the methods used for randomization adequate? Can't tell
NR		Comparator: Placebo (SQ saline injections)	NR	6. Were methods for allocation concealment adequate? Can't tell
Outcome assessment:				7. Were incomplete outcome data adequately addressed? Yes
NR				8. Was intention to treat analysis used? No
Total number randomized:				9. Was the differential loss to followup between the compared groups low (< 10%)? No
82 (82)				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
Wilson, 1992	Publication type: Full text	Inclusion criteria: Patients undergoing elective TKR with BiometAGC 2500 or Insall-Burnstein prostheses and a standard technique	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: UK	Exclusion criteria: NR	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: NR	Intervention: VFP (A-V Impulse System) fitted to the operated limb postoperatively and used continuously (except during mobilization) until ascending ipsilateral venography performed on 9 th or 10 th post-operative day	Final: PE, fatal PE, non-fatal PE (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Comparator: Control	Intermediate: DVT, proximal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: NR		Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Partially
	Outcome assessment: All venograms were independently assessed blind			5. Were the methods used for randomization adequate? Can't tell
	Total number randomized: 59 (59)			6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to

				<p>followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Bailey, 1991	<p>Publication type: Full text</p> <p>Geographic location: USA</p> <p>Funding: Industry</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Randomized to 1 of 2 treatment regimens using a standard computerized randomization program</p> <p>Outcome assessment: All venograms were carried out and interpreted by physicians blinded to the patients' treatment group</p> <p>Total number randomized (number randomized in arms of interest): 95 (95)</p>	<p>Inclusion criteria: Age≥40y scheduled for elective primary or revision THA</p> <p>Exclusion criteria: Active peptic ulcer disease; allergy to iodine contrast dye; underlying bleeding disorders; hx of CVAs, previous venous disease or hx or venous surgery</p> <p>Intervention 1: Low dose warfarin orally starting with 10mg the evening before surgery (adjusted to 7.5mg for women >70 and minor abnormal LFTs) and 5mg on the day of the surgery if PT and TT<15s. Subsequent doses adjusted to maintain PT of 14-18s</p> <p>Intervention 2: IPC (Kendall, Inc.) applied immediately after surgery in the recovery room and continuously except during bathing and physical therapy until hospital discharge</p>	<p>Duration of followup: Post-operative</p> <p>Followup: 100% in both arms</p> <p>Final: Mortality, mortality due to bleeding (post-operative)</p> <p>Intermediate: DVT, proximal DVT (post-operative)</p> <p>Adverse events: Readmission</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Eriksson,	Publication type:	Inclusion criteria:	Duration of followup:	<p>Overall quality rating: Good</p> <p>1. Were the groups similar at baseline in terms of baseline</p>

1991	Full text	Patients admitted for THR ≥ 40y	Post-operative	characteristics and prognostic factors? Yes
	Geographic location: Sweden	Exclusion criteria: Allergy to iodine or contrast medium; already receiving anticoagulant treatment; renal insufficiency; elevated levels of liver enzymes; hx of bleeding disorders, liver or renal disease; cerebral hemorrhage <6m before the time of the study; hypersensitivity to heparin or iodine; previous inclusion in the study	Followup: DVT: Dalteparin 94% UFH 86% PE: Dalteparin 97% UFH 90%	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government/Foundation			3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers: NR		Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding; mortality (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Allocated to one of the two treatment groups in a randomized manner	Intervention 1: Dalteparin 5000 IU SQ QD starting evening before surgery for 10d postoperatively Intervention 2: UFH 5000 IU SQ TID starting 2h before surgery for 10d postoperatively	Intermediate: DVT, asymptomatic DVT, symptomatic DVT (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All phlebograms were made and analyzed by two experienced radiologists who were unaware of the assigned treatment. The pulmonary scintiscans were evaluated by an experienced clinical physiologist who was unaware of the phlebographic findings and the particular prophylactic treatment		Adverse events: Major bleeding, major bleeding leading to re-operation (post-operative)	6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? No
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair
Jorgensen , 1991	Publication type: Full text	Inclusion criteria: Patients undergoing elective knee arthroplasty (primary or revision)	Duration of followup: post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Denmark	Exclusion criteria: Patients receiving antithrombic medications; premenopausal women; history of venous thromboembolic disease; allergy to	Followup: 81.25% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding:		Final:	3. Were subjects and providers

Industry, government/foundation	radioopaque contrast media	Nonfatal PE (post-operative)	blind to the intervention status of participants? No
Number of centers: 1	Intervention 1: General anesthesia: Induction: thiopentone 3-5mg/kg, following intubation, lungs were ventilated with 66% NO in oxygen and diazepam 0.2mg/kg administered IV	Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
Randomization and allocation concealment: NR	Intervention 2: Extradural anesthesia: 2% mepivacaine 3mL with adrenaline followed by 2% mepivacaine 8-15 mL through a lumbar extradural catheter. After surgery, 0.25% bupivacaine 5mL/hr was infused through the extradural catheter by infusion pump	Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
Outcome assessment: Venograms were scrutinized by the same two experienced radiologist unaware of the anesthetic agent used			6. Were methods for allocation concealment adequate? Can't tell
Total number randomized (number randomized in arms of interest): 48 (48)			7. Were incomplete outcome data adequately addressed? Yes
			8. Was intention to treat analysis used? Yes
			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
			10. Was the overall loss to followup low (< 20%)? Yes
			11. Conflict of interest reported and insignificant? Yes
Lassen, 1991	Publication type: Full text	Duration of followup: post-operative	Overall quality rating: Fair
Geographic location: Denmark	Inclusion criteria: > 40y; scheduled for elective hip replacement	Followup: Tinzaparin 88.6%; placebo 92.4%	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
Funding: NR	Exclusion criteria: Treated with plasma expanders or investigational drugs within 4w prior to the operation; impaired renal or hepatic function; uncontrolled HTN (diastolic pressure >120mmHg); hemorrhagic diasthesis; pregnancy; confinement to bed; revision arthroplasty; hypersensitivity to radio-opaque dye, heparin, bisulfite, or benzyl alcohol; ongoing anticoagulant therapy; lack of informed consent	Final: PE, Fatal PE, non-fatal (postoperatively); mortality (in-hospital)	2. Were outcomes assessed using a valid methodology and criteria? Yes
Number of centers: 2	Intervention: Tinzaparin 50 units anti-Xa/kg SQ daily starting 2h pre-operatively for 7d	Intermediate: DVT, asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT (postoperatively)	3. Were subjects and providers blind to the intervention status of participants? Yes
Randomization and allocation concealment: Random numbers		Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Partially
Outcome assessment:			5. Were the methods used for randomization adequate? Yes
			6. Were methods for allocation concealment adequate? Can't tell
			7. Were incomplete outcome data adequately addressed? Yes
			8. Was intention to treat analysis

	All venograms evaluated by a radiologist who was unaware of the randomization results	Comparator: Placebo (SQ saline injections)		used? No 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
	Total number randomized: 210 (210)			
Levine, 1991	<p>Publication type: Full text</p> <p>Geographic location: Canada</p> <p>Funding: Government/Foundation</p> <p>Number of centers: NR</p> <p>Randomization and allocation concealment: Randomized stratification by hospital, hx of documented VTE (present, absent) and by type of prosthesis (cement or uncemented)</p> <p>Outcome assessment: All venograms and bleeding episodes were interpreted by a central committee that was blinded to patients assigned treatment</p> <p>Total number randomized (number randomized in arms of interest):</p>	<p>Inclusion criteria: Consecutive patients undergoing elective hip replacement</p> <p>Exclusion criteria: < 40y; hx of underlying bleeding disorder; allergy to iodine or radiopaque dye; severe hepatic or renal disease; hx of MI or stroke < previous 6m; underlying psychiatric or addictive disorder; required to receive aspirin, long-term oral anticoagulant therapy, NSAIDs, indomethacin or other antiplatelet therapy during hospitalization</p> <p>Intervention 1: Enoxaparin 30mg SQ BID, starting 12-24h postoperatively and continued for 14d, or until discharge if it occurred sooner</p> <p>Intervention 2: UFH 7500 U SQ BID, starting 12-24h postoperatively and continued for 14d, or until discharge if it occurred sooner</p>	<p>Duration of followup: Postoperative</p> <p>Followup: 100% in both arms</p> <p>Final: Fatal PE, nonfatal PE, PE, mortality, mortality due to bleeding (post-operative)</p> <p>Intermediate: DVT, proximal DVT (post-operative)</p> <p>Adverse events: Major bleeding, minor bleeding, HIT (post-operative)</p>	<p>Overall quality rating: Good</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? No</p> <p>Overall quality rating: Fair</p>

Mitchell, 1991	665 (665)			
	Publication type: Full text	Inclusion criteria: Age > 40y; normal hematological, renal, and nutritional parameters; history of osteoarthritis or rheumatoid arthritis with no previous surgery on the affected knee	Duration of followup: Postoperative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: USA		Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Unknown	Exclusion criteria: Malignancy, history of DVT or PE	Final: NR	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Intervention 1: General anesthesia: Induction: sodium thiopental; maintenance: halogenated agent and nitrous oxide in oxygen	Intermediate: Proximal DVT(post-operative)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: Patients were randomized prospectively based on their hospital number to receive either an epidural or general anesthetic	Intervention 2: Epidural anesthesia: local anesthetic was then injected to obtain an anesthetic level adequate for the surgical procedure. Sedation was provided by incremental doses of intravenous narcotic and/or benzodiazepine	Adverse events: NR	5. Were the methods used for randomization adequate? No
	Outcome assessment: bilateral contrast venography and ventilation-perfusion scanning were performed on the sixth, seventh, and eighth postoperative days and interpreted in a blinded fashion			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 72 (72)			7. Were incomplete outcome data adequately addressed? Yes
Planes, 1991	Publication type: Full text	Inclusion criteria: Age ≥ 45y; weighing ≥ 45 kg; undergoing elective hip replacement	Duration of followup: Post-operative	8. Was intention to treat analysis used? Yes
	Geographic location: France	Exclusion criteria: Latent bleeding disorder; known allergy to iodine or radiopaque dye; renal insufficiency; previous replacement of the same hip; anticoagulant or antiplatelet therapy during the 8d prior to surgery; unable or unwilling to	Followup: 100% in all arms	9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
	Funding: Unknown		Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding,	10. Was the overall loss to followup low (< 20%)? Yes
	Number of centers: 1			11. Conflict of interest reported and insignificant? No
				Overall quality rating: Fair

	<p>Randomization and allocation concealment: NR</p> <p>Outcome assessment: All venograms were examined by two experienced consultant radiologists without knowledge of group assignment.</p> <p>Total number randomized (number randomized in arms of interest): 194 (194)</p>	<p>undergo general or spinal anesthesia</p> <p>Intervention 1: General anesthesia induced by fentanyl and thiopentone + enoxaparin 40 mg SQ 12 h prior to surgery, 12h after surgery then daily</p> <p>Intervention 2: Spinal anesthesia administered at the L3-L4 level + enoxaparin 20mg SQ 1h after onset of anesthesia then 40mg 12h after surgery and daily. Droperidol and/or midazolam were administered IV when sedation was necessary</p> <p>Intervention 3: Spinal anesthesia + enoxaparin 40mg SQ 12h after surgery then daily</p>	<p>mortality (post-operative)</p> <p>Intermediate: Proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: Major bleeding, minor bleeding (post-operative)</p>	<p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p>
Torholm, 1991	<p>Publication type: Full text</p> <p>Geographic location: Denmark</p> <p>Funding: NR</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: NR</p> <p>Outcome assessment: NR</p>	<p>Inclusion criteria: THR patients \geq 40y</p> <p>Exclusion criteria: Bleeding disorders; hepatic or renal insufficiency; previous septic endocarditis; cerebral hemorrhage during the past 6m; hypersensitivity to heparin or iodine; anticoagulant therapy within 1w of surgery</p> <p>Intervention: Dalteparin 2500 IU SQ 2h before surgery and 12h after surgery, then 5000 IU SQ daily for 6d</p> <p>Comparator: Placebo (SQ saline injections)</p>	<p>Duration of followup: Post-operative</p> <p>Followup: Dalteparin 96.7%; placebo 90%</p> <p>Final: Mortality, mortality due to bleeding (post-operative)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? No</p> <p>9. Was the differential loss to</p>

Total number randomized:
120 (120)

followup between the compared groups low (< 10%)? Yes
10. Was the overall loss to followup low (< 20%)? Yes
11. Conflict of interest reported and insignificant? Yes

Overall quality rating: Fair

Woolson,
1991

Publication type:
Full text

Inclusion criteria:
Primary or revisions THR patients >39y

Duration of followup:
Post-operative

Geographic location:
USA

Exclusion criteria:
Allergy to aspirin or warfarin; recently had a peptic ulcer or other bleeding diathesis; taken any drug that affect platelet function within two weeks before operation; expected to remain in bed for more than 4d postoperatively

Followup:
100% in all arms

Funding:
Unfunded

Final:
PE (post-operative)

Number of centers:
1

Intermediate:
Proximal DVT (post-operative)

Randomization and allocation concealment:
Random assignment to groups was carried out with the use of sealed envelopes

Intervention 1:
IPC (Sequential Compression Device) thigh-high, worn bilaterally during surgery and until screening for DVT + aspirin 650mg po BID beginning the evening before surgery

Adverse:
NR

Outcome assessment:
NR

Intervention 2:
IPC (Sequential Compression Device) thigh-high, worn bilaterally during surgery and until screening for DVT + warfarin 7.5mg or 10mg po the evening before surgery then adjusted according to prothrombin time to 1.2 to 1.3 X the control

Total number randomized:
196 (196)

Comparator:
IPC (Sequential Compression Device) thigh-high, worn bilaterally during surgery and until screening for DVT

1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
2. Were outcomes assessed using a valid methodology and criteria? Yes
3. Were subjects and providers blind to the intervention status of participants? No
4. Were outcome assessors blind to exposure/intervention status? Cant' tell
5. Were the methods used for randomization adequate? Yes
6. Were methods for allocation concealment adequate? Yes
7. Were incomplete outcome data adequately addressed? Yes
8. Was intention to treat analysis used? Yes
9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
10. Was the overall loss to followup low (< 20%)? Yes
11. Conflict of interest reported and insignificant? Yes

Overall quality rating: Fair

Haas,
1990

Publication type:
Full text

Inclusion criteria:
>39y scheduled for primary unilateral or one

Duration of followup:
Post-operative

1. Were the groups similar at baseline in terms of baseline

	Geographic location: USA	stage bilateral TKA	Followup: 100% in both arms	characteristics and prognostic factors? Yes
	Funding: NR	Exclusion criteria: Hx of PE; receiving anticoagulant; hx of allergy to aspirin or massive bleeding in the stomach or duodenum	Final: NR	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Intervention 1: IPC (Kendall, Inc.) placed on the uninvolved limb just before surgery and on the operated limb after the surgery, worn continuously and removed only for washing or when patient was walking until morning after post-operative lung scan	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: Randomized to 2 treatment groups		Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Yes
	Outcome assessment: All venograms were interpreted by 1 radiologist unaware of the prophylactic regimen	Intervention 2: Aspirin 650mg PO BID starting day before surgery and continued until patient was discharged from the hospital		5. Were the methods used for randomization adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 119 (119)			6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
				Overall quality rating: Fair
Sorensen, 1990	Publication type: Full text	Inclusion criteria: Patients aged ≥ 40 y undergoing THR	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Can't tell
	Geographic location: Denmark	Exclusion criteria: NR	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: NR	Intervention: Tinzaparin 50 anti-Xa U/kg SQ daily starting 2h before surgery and continued for 7 consecutive days	Final: Mortality, mortality due to bleeding (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Can't tell
	Number of centers: 1	Comparator:	Intermediate: DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status?

	Randomization and allocation concealment: NR	Placebo (SQ saline injections)	Adverse events: NR	Can't tell 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? No 8. Was intention to treat analysis used? No 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
	Outcome assessment: NR			
	Total number randomized (number randomized in arms of interest): 70 (70)			
Dechavanne, 1989	Publication type: Full text Geographic location: France Funding: NR Number of centers: 2 Randomization and allocation concealment: Randomly allocated to 1 of 3 treatment groups using a sealed envelope Outcome assessment: NR	Inclusion criteria: >40y undergoing elective hip replacement under general anesthesia Exclusion criteria: Hemorrhagic diathesis; severe hepatic or renal insufficiency; active peptic ulcer disease; taking aspirin or drugs known to affect platelet function during 2 days prior to surgery Intervention 1: Dalteparin 2500 anti-Xa U SQ q12h starting 2h before surgery for 10-13d post-operative Intervention 2: Dalteparin 2500 anti-Xa U for the first 48h followed by 5000 anti-Xa U QD SQ starting 2h before surgery for 10-13d post-operative Intervention 3: Heparin 5000 IU SQ twice daily with dose	Duration of followup: Post-operative Followup: 100% in both arms Final: NR Intermediate: DVT, proximal DVT, distal DVT (post-operative) Adverse events: NR	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? Can't tell 4. Were outcome assessors blind to exposure/intervention status? Can't tell 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes

	Total number randomized (number randomized in arms of interest): 124 (124)	adjusted after 2 nd d according to APTT starting 2h before surgery for 10-13d post-operative		<p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? No</p>
Monreal, 1989	<p>Publication type: Full text</p> <p>Geographic location: Spain</p> <p>Funding: NR</p> <p>Number of centers: NR</p> <p>Randomization and allocation concealment: Allocated by numbers from a randomization list; sealed envelope guaranteed that in case of emergency, type of prophylaxis could be checked without breaking code for other patients</p> <p>Outcome assessment: NR</p> <p>Total number randomized (number randomized in arms of interest): 90 (90)</p>	<p>Inclusion criteria: >40y admitted for HFS on the day of fracture</p> <p>Exclusion criteria: Underlying bleeding disorder</p> <p>Intervention1: Dalteparin 2,500U SQ 2h before surgery followed by 5000 U SQ QD for 9d post-operative</p> <p>Intervention2: Heparin 5000 U SQ starting 2h before surgery and q8h for 9d post-operative</p>	<p>Duration of followup: Post-operative</p> <p>Followup: PE: 100% in both arms DVT: Dalteparin 69.57% Heparin 68.18%</p> <p>Final: Fatal PE, nonfatal PE, PE, mortality due to bleeding, mortality (post-operative)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? No</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? No</p> <p>11. Conflict of interest reported and insignificant? No</p> <p>Overall quality rating: Fair</p> <p>1. Were the groups similar at</p>
Powers,	Publication type:	Inclusion criteria:	Duration of followup:	

1989	Full text	18-90y; entering hospital for HFS	90d	baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Canada	Exclusion criteria: Allergy to aspirin, warfarin or radiopaque dye; inability to undergo I-25 fibrinogen leg scanning or impedance plethysmography; medical need to continue aspirin or other antiplatelet therapy; could not be randomized within 24h of hospital admission with fractured hip; refused to give informed consent	Followup: 100% in all arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Industry; government		Final: PE, fatal PE, non-fatal PE, mortality due to bleeding (21d); mortality (90d)	3. Were subjects and providers blind to the intervention status of participants? Partially
	Number of centers: 3		Intermediate: NR	4. Were outcome assessors blind to exposure/intervention status? Partially
	Randomization and allocation concealment: Patients were allocated using sealed envelopes to treatment groups, according to a prescribed randomized arrangement, balanced in blocks of 3 and 6	Intervention 1: Warfarin 10mg PO given after surgery up to 21d postoperatively or discharge whichever occurred first;	Adverse events: Major bleeding (postoperatively)	5. Were the methods used for randomization adequate? Yes
	Outcome assessment: All diagnostic results and suspected hemorrhagic complications were adjudicated by an independent panel unaware of treatment allocation.	Intervention 2: EC-aspirin 650mg PO BID starting postoperatively up to 21d or discharge whichever occurred first		6. Were methods for allocation concealment adequate? Yes
		Comparator: Placebo		7. Were incomplete outcome data adequately addressed? Yes
	Total number randomized: 194 (194)			8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? Yes
Planes, 1988	Publication type: Full text	Inclusion criteria: Age >45y and undergoing elective hip replacement	Duration of followup: Post-operative	Overall quality rating: Good
	Geographic location: France	Exclusion criteria: Underlying bleeding disorder; hx of allergy to iodine or radiopaque dye; renal insufficiency with Cr >30mg/l; hx of DVT associated with previous hip surgery; hx of replacement of the same hip, or taken anticoagulant or antiplatelet therapy during the 8d prior to	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: Unknown		Final: Fatal, non- fatal PE, mortality due to bleeding, mortality (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers:			3. Were subjects and providers blind to the intervention status of participants? Yes
				4. Were outcome assessors blind

7		surgery.	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	to exposure/intervention status? Yes
	Randomization and allocation concealment: NR	Intervention 1: Enoxaparin 40mg SQ, QD, started 12h before surgery, and continued until 14d or hospital discharge	Adverse events: Major bleeding, minor bleeding (postoperative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: All venograms interpreted by central committee of 3 radiologists independently without knowledge of treatment assignment	Intervention 2: UFH 5000IU SQ, q8h daily, started 12h before surgery, and continued until 14d or hospital discharge		6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 237 (237)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
Barre, 1987	Publication type: Full text	Inclusion criteria: Age≥40y who had to undergo THR under epidural anesthesia	Duration of followup: 60d	Overall quality rating: Good
	Geographic location: France	Exclusion criteria: Hemorrhagic past history; severe hepatic or renal insufficiency; femoral neck fracture; progressive cancer	Followup: 100% in both arms	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Funding: NR		Final: Mortality, mortality due to bleeding, PE, nonfatal PE, fatal PE (60d)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: NR	Intervention 1: Dalteparin 2,500 anti-Xa U SQ 2h before surgery, continued q12h postoperatively for 10d	Intermediate: DVT (post-operative)	3. Were subjects and providers blind to the intervention status of participants? No
	Randomization and allocation concealment: Randomly allocated to treatment groups	Intervention 2: Heparin 3750 IU SQ 2h before surgery, continued q8h postoperatively for 10d with dose adjustment using thrombin time and/or cephalin plus activator time	Adverse events: NR	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Outcome assessment: NR			5. Were the methods used for randomization adequate? Can't tell
				6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes

	Total number randomized (number randomized in arms of interest): 80 (80)			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No
Paiement, 1987	Publication type: Full text Geographic location: USA Funding: Industry, government/foundation Number of centers: 1 Randomization and allocation concealment: NR Outcome assessment: The radiologists who interpreted the phlebography were unaware of the prophylactic regimen used. Total number randomized (number randomized in arms of interest): 163 (163)	Inclusion criteria: Age >39y and undergoing total hip replacement Exclusion criteria: Patients found before or at operation to require more than 3 weeks of postoperative bed rest because of the complexities of the operation were excluded. Intervention 1: Low dose warfarin started the night before surgery, then 5 mg on the night of surgery adjusted to maintain PTT for control at 11-12 s, and continued until at least 2d after radiographic phlebography, if the result was negative Intervention 2: IPC (Gaymar) started postoperatively in the recovery room and worn bilaterally continuously, except during brief periods of skin care and when the patient was ambulating	Duration of followup: Post-operative Followup: 100% in both arms Final: Fatal PE, nonfatal PE, PE (post-operative) Intermediate: DVT, proximal DVT, distal DVT (post-operative) Adverse events: Major bleeding, minor bleeding (postoperative)	Overall quality rating: Fair 1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to exposure/intervention status? Yes 5. Were the methods used for randomization adequate? Can't tell 6. Were methods for allocation concealment adequate? Can't tell 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? Yes
Alfaro,	Publication type:	Inclusion criteria:	Duration of followup:	Overall quality rating: Fair 1. Were the groups similar at

1986	Full text	> 40y; admitted for THR and gave informed consent	Post-operative (minimum 7d)	baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Spain	Exclusion criteria: Pregnancy; history of peptic ulcers; hematemesis or sensitivity to salicylates; ingested aspirin or other antiplatelet agent in week prior to admission	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government		Final: PE (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Can't tell
	Number of centers: 1	Intervention 1: Aspirin 500mg PO BID beginning preoperatively for 7d	Intermediate: DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: NR	Intervention 2: Aspirin 125mg PO BID beginning preoperatively for 7d	Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: NR	Comparator: Control		6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 120 (90)			7. Were incomplete outcome data adequately addressed? Can't tell
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Poor
Turpie, 1986	Publication type: Full text	Inclusion criteria: ≥40y undergoing elective hip replacement.	Duration of followup: Post-operative	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Canada	Exclusion criteria: Underlying bleeding disorder; history of allergy to iodine or radiopaque dye; DVT related to hip surgery; surgery on ipsilateral hip; taking aspirin during hospitalization; previous VTE; previous hip surgery	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government/foundation		Final: PE, fatal PE, nonfatal PE, mortality due to bleeding, mortality (post-operative)	3. Were subjects and providers blind to the intervention status of participants? Yes
	Number of centers:	Intervention:		4. Were outcome assessors blind

McKenzie, 1985	Multicenter	Enoxaparin 30mg SQ BID starting 12-24h after surgery for 14d or until discharge	Intermediate: DVT, proximal DVT (post-operative)	to exposure/intervention status? Partially
	Randomization and allocation concealment: NR	Comparator: Placebo (SQ saline injection)	Adverse events: Major bleeding, minor bleeding (post-operative)	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: Venograms and bleeding episodes were interpreted by a central committee unaware of the assigned treatment			6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 100 (100)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
				Overall quality rating: Good
	Publication type: Full text	Inclusion criteria: Patients admitted for HFS	Duration of followup: 365d postoperatively	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: UK	Exclusion criteria: NR	Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Unknown	Intervention 1: General anesthesia: Induced with althesin 1-3ml IV, following the administration of suxamethonium 50mg, the trachea was intubated with a cuffed endotracheal tube and anesthesia was maintained with 66% nitrous oxide and 0.75-1.25% halothane in oxygen	Final: Mortality (365d)	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Intervention 2: Subarachnoid blockade: Hyperbaric cinchocaine 1.2-1.5ml injected slowly to the subarachnoid space at the L3-4 or L4-5 space via a 22-gauge spinal needle. The block was performed with the patient in the horizontal lateral position with fractured hip	Intermediate: DVT, symptomatic DVT, asymptomatic DVT (post-operative)	4. Were outcome assessors blind to exposure/intervention status? Can't tell
	Randomization and allocation concealment: Patients allocated randomly to received subarachnoid blockade or general anesthesia		Adverse events: NR	5. Were the methods used for randomization adequate? Can't tell
	Outcome assessment: NR			6. Were methods for allocation concealment adequate? Can't tell
				7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes

	Total number randomized (number randomized in arms of interest): 40 (40)	dependent. Small doses of diazepam were administered IV if sedation was necessary.		<p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? No</p>
Welin-Berger, 1982	<p>Publication type: Full text</p> <p>Geographic location: Sweden</p> <p>Funding: Government / foundation</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: NR</p> <p>Outcome assessment: NR</p> <p>Total number randomized: 60 (40)</p>	<p>Inclusion criteria: THR; no history of previous DVT and with normal venous outflow capacity of both legs determined pre-operatively</p> <p>Exclusion criteria: NR</p> <p>Intervention: Heparin 5000IE SQ preoperatively and repeated every 12h during 1st post-operative week</p> <p>Comparator: Control</p>	<p>Duration of followup: Post-operative</p> <p>Followup: 100% in both arms</p> <p>Final: PE (post-operative)</p> <p>Intermediate: DVT (post-operative)</p> <p>Adverse events: NR</p>	<p>Overall quality rating: Fair</p> <p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? No</p> <p>4. Were outcome assessors blind to exposure/intervention status? Can't tell</p> <p>5. Were the methods used for randomization adequate? Can't tell</p> <p>6. Were methods for allocation concealment adequate? Can't tell</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? No</p>
Modig,	Publication type:	Inclusion criteria:	Duration of followup:	<p>Overall quality rating: Poor</p> <p>1. Were the groups similar at</p>

1981	Full text	Severe osteoarthritis of the hip joint and undergoing THR; no history of heart or lung disease, diabetes, previous thromboembolism, varicose veins, or leg ulcers	14d	baseline in terms of baseline characteristics and prognostic factors? Yes
	Geographic location: Sweden		Followup: 100% in both arms	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Funding: Government/Foundation; industry	Exclusion criteria: NR	Final: PE (14d)	3. Were subjects and providers blind to the intervention status of participants? No
	Number of centers: 1	Intervention 1: General anesthesia: Artificial ventilation with nitrous oxide/oxygen via an endotracheal tube and intravenously administered fentanyl and pancuronium bromide, narcotic analgesics were given intramuscularly on demand for pain relief	Intermediate: DVT, proximal DVT, distal DVT (14d)	4. Were outcome assessors blind to exposure/intervention status? Yes
	Randomization and allocation concealment: The patients were randomly allotted, according to their date of birth		Adverse events: NR	5. Were the methods used for randomization adequate? No
	Outcome assessment: All phlebograms were scrutinized by an experienced radiologist unaware of the type of anesthetic regimen used in any particular patient.	Intervention 2: Epidural anesthesia: Bupivacaine with epinephrine prolonged into the postoperative period for pain relief		6. Were methods for allocation concealment adequate? Can't tell
	Total number randomized (number randomized in arms of interest): 30 (30)			7. Were incomplete outcome data adequately addressed? Yes
				8. Was intention to treat analysis used? Yes
				9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
				10. Was the overall loss to followup low (< 20%)? Yes
				11. Conflict of interest reported and insignificant? No
McKenna, 1980	Publication type: Full text	Inclusion criteria: Patients aged >40y admitted for TKR	Duration of followup: Post-operative	Overall quality rating: Fair
	Geographic location: USA	Exclusion criteria: History of DVT or PE in the 6m prior to study	Followup: Aspirin 81.82%; Placebo 100%	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Can't tell
	Funding: NR	Intervention: Aspirin 325mg PO TID immediately after admission and continued until discharge	Final: Mortality, mortality due to bleeding (post-operative)	2. Were outcomes assessed using a valid methodology and criteria? Yes
	Number of centers: 1	Comparator:		3. Were subjects and providers blind to the intervention status of participants? Can't tell
				4. Were outcome assessors blind

Randomization and allocation concealment: Computer-generated random number table	Placebo (tablet)	Intermediate: DVT, proximal DVT, distal DVT (post-operative)	to exposure/intervention status? Can't tell
Outcome assessment: NR		Adverse events: NR	5. Were the methods used for randomization adequate? Yes
Total number randomized (number randomized in arms of interest): 46 (21)			6. Were methods for allocation concealment adequate? Yes
			7. Were incomplete outcome data adequately addressed? Yes
			8. Was intention to treat analysis used? No
			9. Was the differential loss to followup between the compared groups low (< 10%)? Yes
			10. Was the overall loss to followup low (< 20%)? Yes
			11. Conflict of interest reported and insignificant? No
			Overall quality rating: Fair

*Duration of followup is reported as the original study's longest reported followup for outcomes of interest and followup percent is reported for the study's pre-specified primary outcome

† A=Patient operated within 12h of randomization, B= Patient operated 12-24h after randomization. C= Patient operated >24h after randomization. D= Patient operated within 8h of randomization. E= Patient operated >8h after randomization.

Abbreviations: ALT=Alanine aminotransferase; APTT= activated partial thromboplastin time; ARF=acute renal failure; AST=aspartate aminotransferase; BID= twice daily; BMI=body mass index ; CHF=congestive heart failure; CI=contraindication; CNS=central nervous system; Cr=creatinine; CRF=chronic renal failure; CT=computed tomography scan; CUS=continuous ultrasonography; CVA= cerebraovascular accident; CVI= chronic venous insufficiency; d=day(s); dL=deciliter; DUS= Doppler ultrasound; DVT=deep vein thrombosis; EC=enteric coated; GA=general anesthesia; GCS=graduated compression stocking; GI=gastrointestinal; h=hour(s); HFS=hip fracture surgery; HIT=heparin-induced thrombocytopenia; HTN=hypertension; hx=history; INR=international normalized ratio; IPC=intermittent pneumatic compression; IU=international units; IV=intravenous; IVC=inferior vena cava; kg=kilograms; L=liter; LMWH=low molecular weight heparin; m=months; MC=multicenter; MI=myocardial infarction; min=minute(s); mg=milligrams; mmHg=millimeters of mercury; mL=milliliters; MRI=magnetic resonance imaging; NR=not reported; NSAID=nonsteroidal anti-inflammatory drug; NYHA=New York heart association PE=pulmonary embolism; PO=by mouth; PT=prothrombin time; PTS=post thrombotic syndrome; PVD=peripheral vascular disease; QD=daily; SCr= serum creatinine; SQ=subcutaneously; TCP=thrombocytopenia; THA=total hip arthroplasty; TKA=total knee arthroplasty; THR=total hip replacement; TKR=total knee replacement; TT=thromboplastin time; UFH=unfractionated heparin; UK=United Kingdom; ULN=upper limit of normal; US=ultrasound; USA=United States of American; VFP=venous foot pump; VTE=venous thromboembolism; VQ=ventilation perfusion; w=week(s); y=year(s)

Table 4. Quality and characteristics of randomized controlled trials evaluating nonmajor orthopedic surgery

Study, year	Trial characteristics	Population and interventions	Followup and Outcomes of interest (Timing)	Quality assessment
Lapidus, 2007	<p>Publication type: Full text</p> <p>Geographic location: Sweden</p> <p>Funding: Industry/Government</p> <p>Number of centers: 1</p> <p>Randomization and allocation concealment: Patients were consecutively included and randomized (by computer) into the study immediately after surgery at the outpatient surgery unit.</p> <p>Outcome assessment: The radiologist on duty made a preliminary evaluation of the phlebography for clinical purposes. A standardized, secondary evaluation was then carried out by an experienced independent radiologist blinded to the randomization and previous phlebographic findings.</p> <p>Total number randomized (number randomized in arms of interest): 105 (105)</p>	<p>Inclusion criteria: Patients age 18 to 75 years with acute (0-72h) Achilles tendon rupture accepted for surgery admitted</p> <p>Exclusion criteria: Inability or refusal to give informed consent for participation in the study, ongoing treatment with anticoagulant therapy, known allergy for contrast media, intended followup at another hospital, an inability to comply with the study instructions (because of drug or alcohol abuse, cognitive dysfunction, etc), known kidney disorder, a recent thromboembolic event (during the preceding 3 months), recent surgery (during the preceding month), the presence of known malignancy, a current bleeding disorder, pregnancy, treatment with high doses of acetylsalicylic acid (325 mg) other platelet inhibitors, and other injuries</p> <p>Intervention 1: Dalteparin 5000 units SC QD started a few hours after surgery and continued until hospital discharge for a total duration of 6 weeks</p> <p>Intervention 2: Placebo (sodium chloride) injections SC QD started a few hours after surgery and continued until hospital discharge for a total duration of 6 weeks</p>	<p>Duration of followup: 42d</p> <p>Followup: 100% in all arms</p> <p>Final: PE, Fatal PE, Non-fatal PE (42d)</p> <p>Intermediate: DVT, proximal DVT (42d)</p> <p>Adverse events: Major bleeding (42d)</p>	<p>1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes</p> <p>2. Were outcomes assessed using a valid methodology and criteria? Yes</p> <p>3. Were subjects and providers blind to the intervention status of participants? Yes</p> <p>4. Were outcome assessors blind to exposure/intervention status? Yes</p> <p>5. Were the methods used for randomization adequate? Yes</p> <p>6. Were methods for allocation concealment adequate? Yes</p> <p>7. Were incomplete outcome data adequately addressed? Yes</p> <p>8. Was intention to treat analysis used? Yes</p> <p>9. Was the differential loss to followup between the compared groups low (< 10%)? Yes</p> <p>10. Was the overall loss to followup low (< 20%)? Yes</p> <p>11. Conflict of interest reported and insignificant? Yes</p> <p>Overall quality rating: Good</p>

Study, year	Trial characteristics	Population and interventions	Followup and Outcomes of interest (Timing)	Quality assessment
Michot, 2002	Publication type: Full text Geographic location: Switzerland Funding: Unknown Number of centers: 1 Randomization and allocation concealment: Sealed envelopes Outcome assessment: NR Total number randomized (number randomized in arms of interest): 130 (130)	Inclusion criteria Patients aged 18 to 80 years referred for diagnostic or therapeutic arthroscopic knee surgery Exclusion criteria Inability or unwillingness to give written informed consent; history of DVT or PE; known deficiency of antithrombin III, protein C, protein S, or presence of a resistance to activated protein C; malignancy; pregnancy; ongoing treatment with steroids, anticoagulant or antiplatelet agents, long-term use of NSAIDs; hypersensitivity to heparin; history of GI bleeding in the past 2 weeks; history of cerebrovascular accident in the past 6 months; or severe renal or hepatic failure Intervention 1: Dalteparin 2500 units for patients 70kg or less and Dalteparin 5000 units for patients over 70kg given SC QD starting 60-120 mins before operation for 30d Intervention 2: No prophylaxis (Control group)	Duration of followup: 30d Followup: 100% Final: PE (30d) Intermediate: DVT, proximal DVT, distal DVT (30d) Adverse events: Major bleeding, minor bleeding (30d)	1. Were the groups similar at baseline in terms of baseline characteristics and prognostic factors? Yes 2. Were outcomes assessed using a valid methodology and criteria? Yes 3. Were subjects and providers blind to the intervention status of participants? No 4. Were outcome assessors blind to exposure/intervention status? Can't tell 5. Were the methods used for randomization adequate? Yes 6. Were methods for allocation concealment adequate? Yes 7. Were incomplete outcome data adequately addressed? Yes 8. Was intention to treat analysis used? Yes 9. Was the differential loss to followup between the compared groups low (< 10%)? Yes 10. Was the overall loss to followup low (< 20%)? Yes 11. Conflict of interest reported and insignificant? No Overall quality rating: Fair

*Duration of followup is reported as the original study's longest reported followup for outcomes of interest and followup percent is reported for the study's pre-specified primary outcome

Abbreviations: d=day(s); DVT=deep vein thrombosis; GI=gastrointestinal; mins=minutes; PE=pulmonary embolism; QD=once daily; SC=subcutaneously; w=week(s); y=year(s)

Table 5. Quality and characteristics of observational studies

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Bozic, 2010	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Retrospective cohort</p> <p>Funding: Government/Foundation</p> <p>Number of centers: 307</p> <p>Outcome assessment: ICD-9 codes as reported in hospital database</p> <p>Number of participants enrolled: 93,840 (56,642)</p>	<p>Inclusion criteria: ≥18 y; primary TKA as their principal procedure during hospitalization</p> <p>Exclusion criteria: No charges for any VTE prophylaxis treatment; had charges for VTE treatment in formulations representing therapeutic rather than prophylactic anticoagulation</p> <p>Intervention: Warfarin</p> <p>Comparator: Aspirin</p>	<p>Duration of followup (d): 30</p> <p>Covariates/potential confounders adjusted for: Patient characteristics and comorbidities along with propensity score</p> <p>Final: Mortality (30d)</p> <p>Intermediate: NR</p> <p>Adverse: Surgical site bleeding (30d)</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? No 3. Sample size calculated? No 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Partially 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? Yes <p>Overall quality rating: Good</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Gerkens, 2010	<p>Publication type: Full text</p> <p>Geographical location: Belgium</p> <p>Study design: Retrospective cohort</p> <p>Funding: Unknown</p> <p>Number of centers: 20</p> <p>Outcome assessment: ICD-9-CM diagnosis code</p> <p>Number of participants enrolled: 14991 (6937)</p>	<p>Inclusion criteria: THR, TKR, HFS selected from the Medical database using the appropriate ICD-9-CM procedure codes</p> <p>Exclusion criteria: ≤18y; hospitalization records other than the first stay; pre-operative stay >5days</p> <p>Intervention 1: Enoxaparin</p> <p>Intervention 2: Fondaparinux</p> <p>Comparator: No prophylaxis</p>	<p>Duration of followup (d): In hospital</p> <p>Covariates/potential confounders adjusted for: Age, gender, obesity, the risk of bleeding, the type of procedure, the prophylaxis and the hospital for multivariate analysis</p> <p>Final: Mortality, mortality due to bleeding (In-hospital)</p> <p>Intermediate: NR</p> <p>Adverse: Major bleeding (post-procedure)</p>	<p>1. Unbiased selection of the cohort? No</p> <p>2. Selection minimizes baseline differences in prognostic factors? No</p> <p>3. Sample size calculated? No</p> <p>4. Adequate description of the cohort? No</p> <p>5. Validated method to ascertain exposure? Yes</p> <p>6. Validated method for ascertaining clinical outcomes? Partially</p> <p>7. Outcome assessment blinded to exposure? No</p> <p>8. Adequate followup period? No</p> <p>9. Completeness of followup? Yes</p> <p>10. Analysis controls for confounding? Partially</p> <p>Overall quality rating: Poor</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Cusick, 2009	<p>Publication type: Full text</p> <p>Geographical location: Ireland</p> <p>Study design: Prospective</p> <p>Funding: NR</p> <p>Number of centers: 1</p> <p>Outcome assessment: Data recorded prospectively in a database within the orthopedics department by a designated team of outcomes assessment nurses</p> <p>Number of participants enrolled: THR: 2,203 (2,203) TKR: 2,050 (2,050)</p>	<p>Inclusion criteria: Consecutive patients undergoing primary THR or TKR</p> <p>Exclusion criteria: NR</p> <p>Intervention 1: Aspirin 150mg po QD starting postoperative day 1 for 6w</p> <p>Intervention 2: Warfarin</p> <p>Comparator: No prophylaxis</p>	<p>Duration of followup (d): 90</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: Fatal PE, non-fatal PE, mortality (90d)</p> <p>Intermediate: NR</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? No 4. Adequate description of the cohort? No 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Froimson, 2009	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Retrospective</p> <p>Funding: Unfunded</p> <p>Number of centers: 1</p> <p>Outcome assessment: Objectively confirmed pathologies were recorded</p> <p>Number of participants enrolled: 1,810 (1,810)</p>	<p>Inclusion criteria: Consecutive patients 18 to 90y in age; undergoing elective primary or revision hip or knee replacement surgery</p> <p>Exclusion criteria: Patients treated for tumor, fracture, or resection arthroplasty</p> <p>Intervention: IPC (ActiveCare CECT system) applied immediately pre-operatively on contralateral leg the bilateral postoperatively for duration of hospital stay or diagnosis of VTE</p> <p>Comparator: IPC (Flowtron excel pump) applied immediately pre-operatively on contralateral leg the bilateral postoperatively for duration of hospital stay or diagnosis of VTE</p>	<p>Duration of followup (d): 30d</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: Fatal PE, non-fatal PE, mortality, mortality due to bleeding (30d)</p> <p>Intermediate: DVT (30d)</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? No 3. Sample size calculated? No 4. Adequate description of the cohort? Partially 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Gandhi, 2009	<p>Publication type: Full text</p> <p>Geographical location: Canada</p> <p>Study design: Registry</p> <p>Funding: NR</p> <p>Number of centers: 1</p> <p>Outcome assessment: Diagnosis of DVT assessed by a physician, who ordered a Doppler ultrasound based on clinical symptoms of excessive pain and swelling</p> <p>Number of participants enrolled: 1460 (1460)</p>	<p>Inclusion criteria: ≥18 y; primary or secondary osteoarthritis scheduled for primary TKR</p> <p>Exclusion criteria: NR</p> <p>Comparisons: Patients with metabolic syndrome were compared to patients without metabolic syndrome to determine the effect of metabolic syndrome on the incidence of symptomatic DVT</p>	<p>Duration of followup (d): 90d</p> <p>Covariates/potential confounders adjusted for: Adjusted for age, sex, BMI, Charleston Index and education</p> <p>Final: NR</p> <p>Intermediate: Symptomatic DVT (90d)</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? No 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? Yes <p>Overall quality rating: Good</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
McNamara, 2009	<p>Publication type: Full text</p> <p>Geographical location: UK</p> <p>Study design: Prospective observational</p> <p>Funding: NR</p> <p>Number of centers: 1</p> <p>Outcome assessment: All symptomatic DVT confirmed by ultrasound, venography, or at autopsy and all symptomatic PE confirmed by nuclear medicine isotope scan, CT angiography or autopsy</p> <p>Number of participants enrolled: 5300 (5300)</p>	<p>Inclusion criteria: >16 y admitted for HFS</p> <p>Exclusion criteria: Hip fracture treated non-surgically</p> <p>Comparisons: Patients who developed thromboembolic complications were compared to patients who did not develop thromboembolic complications to assess risk factors for symptomatic VTE</p>	<p>Duration of followup (d): 365d</p> <p>Covariates/potential confounders adjusted for: Age, sex</p> <p>Final: Symptomatic VTE (365d)</p> <p>Intermediate: NR</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? No 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? Yes <p>Overall quality rating: Good</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Dorr, 2007	<p>Publication type: Full text</p> <p>Geographical location: USA</p> <p>Study design: Retrospective cohort</p> <p>Funding: Industry</p> <p>Number of centers: 1</p> <p>Outcome assessment: All patients had Doppler ultrasound within 24h before discharge and symptomatic patients suggestive of PE had VQ scan for PE</p> <p>Number of participants enrolled: 970 (970)</p>	<p>Inclusion criteria: Patients who underwent total knee or hip arthroplasties between January 2002 and July 2003</p> <p>Exclusion criteria: NR</p> <p>Comparisons: No/Low risk group was compared to high risk group for the prevalence of thromboembolic complications</p>	<p>Duration of followup (d): 180d</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: Non-fatal PE, mortality (180d)</p> <p>Intermediate: DVT, proximal DVT, distal DVT (180d)</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? No 3. Sample size calculated? No 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Partially 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Shorr, 2007	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Retrospective cohort</p> <p>Funding: Unknown</p> <p>Number of centers: 509</p> <p>Outcome assessment: ICD-9 codes as reported in hospital database</p> <p>Number of participants enrolled: 144,806 (144,860) 257,380† (257,380)†</p>	<p>Inclusion criteria: ≥18 y; primary or secondary diagnosis for hip replacement, knee replacement, or hip fracture surgery during the index hospitalization; received dalteparin, enoxaparin, fondaparinux, or UFH within 1d prior or 2d after hip or knee replacement or hip fracture surgery</p> <p>Exclusion criteria: Received more than 1 anticoagulant of interest on their 1st d of injectable anticoagulant therapy; received UFH only at subtherapeutic prophylactic doses (heparin flush or <5,000 U); admitted diagnosis of VTE [ACS]†; outpatient emergency room or hospital outpatient clinic visit including a VTE diagnosis [ACS diagnosis]† during the 3m prior to initial hospital stay; [no recorded surgery day]†</p> <p>Intervention 1: Fondaparinux</p> <p>Intervention 2: Enoxaparin or dalteparin</p> <p>Intervention 4: UFH</p> <p>Intervention 5:† No prophylaxis</p>	<p>Duration of followup (d): 60d postdischarge</p> <p>Covariates/potential confounders adjusted for: Age†, gender†, orthopedic surgery type†, comorbidities (Charlson-Deyo score)†, LOS†, cancer diagnosis†, number of hospitalizations prior to orthopedic surgery hospitalization†, hospital geographic location (Northeast, West, Midwest, and South)†, hospital type (teaching, non-teaching)†, urban vs. rural hospital location†, and hospital size (number of beds)†</p> <p>Final: Mortality (inhospital)</p> <p>Intermediate: NR</p> <p>Adverse: Major bleeding (60d postdischarge)</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? No 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Partially 6. Validated method for ascertaining clinical outcomes? Partially 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? Partially <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Leirozovicz, 2004 SMART study	<p>Publication type: Full text</p> <p>Geographical location: Bangladesh, China, India, Indonesia, South korea, Malaysia, Pakistan, Phillipines, Singapore, Taiwan, Thailand</p> <p>Study design: Prospective cohort</p> <p>Funding: Industry</p> <p>Number of centers: 39</p> <p>Outcome assessment: DVT was confirmed by ultrasonography and venography, PE was confirmed by VQ scan (PIOPED), angiography, CT scan or autopsy. All outcomes were adjudicated by an independent Committee</p> <p>Number of participants enrolled: 2420 (2420)</p>	<p>Inclusion criteria: Asian patients atleast 40y, hospitalized for THR, TKR or HFS</p> <p>Exclusion criteria: Patients scheduled to receive thromboprophylactic drugs during their hospital stay; patients who received antiplatelet agents or vitamin K antagonists within the week preceding inclusion</p> <p>Comparisons: Patients who developed VTE or sudden death were compared to patients who did not to determine the potential predictive factors</p>	<p>Duration of followup (d): 30d</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: Symptomatic VTE, mortality (30d)</p> <p>Intermediate: NR</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? Yes 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Yes 8. Adequate followup period? No 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Good</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Sachs, 2003	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Controlled observational</p> <p>Funding: Unfunded</p> <p>Number of centers: MC</p> <p>Outcome assessment: Charts screened by nurse-research assistant using standardized tool in duplicate</p> <p>Number of participants enrolled: 1,742 (1,742)</p>	<p>Inclusion criteria: Patients undergoing unilateral primary TKA</p> <p>Exclusion criteria: Bilateral or revision TKA; already on warfarin for chronic AF; selected for warfarin prophylaxis due to previous chronic AF or thromboembolic events</p> <p>Intervention: Warfarin adjusted bi-weekly to maintain INR of 1.6-2.2 for 6w</p> <p>Comparator: No prophylaxis</p>	<p>Duration of followup (d): 90d</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: Mortality (90d)</p> <p>Intermediate: Symptomatic DVT (90d)</p> <p>Adverse: Bleeding leading to transfusion, readmission, reoperation (90d)</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Partially 3. Sample size calculated? No 4. Adequate description of the cohort? Partially 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Ryan, 1998	<p>Publication type: Full text</p> <p>Geographical location: US, Canada</p> <p>Study design: Retrospective cohort</p> <p>Funding: Academia, foundation</p> <p>Number of centers: 4</p> <p>Outcome assessment: Venograms performed postoperatively were interpreted by blinded radiologists and clinically evident bleeding were identified.</p> <p>Number of participants enrolled: 825 (825)</p>	<p>Inclusion criteria: Patients with THR or TKR recruited for one of six prospective studies comparing different antithrombotic prophylaxis regimens</p> <p>Exclusion criteria: <18y; allergic to contrast media; receiving aspirin or long term anticoagulation therapy; underlying bleeding disorder or recent bleeding from GI or urinary tract; pregnancy; SCr>1.7mg/dL; recent eye, ear or CNS surgery; known hypersensitivity to heparin; severe HTN; weight<90lbs</p> <p>Comparisons: Patients with Factor V Leiden mutation was compared to patients without Factor V Leiden mutation to determine its association with DVT and bleeding complications</p>	<p>Duration of followup (d): Postoperative</p> <p>Covariates/potential confounders adjusted for: Age; sex; history of DVT or PE; type of venograms</p> <p>Final: NR</p> <p>Intermediate: DVT (postoperative)</p> <p>Adverse: Major bleeding, minor bleeding (postoperative)</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Yes 3. Sample size calculated? Yes 4. Adequate description of the cohort? Yes 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Partially 8. Adequate followup period? No 9. Completeness of followup? Yes 10. Analysis controls for confounding? Yes <p>Overall quality rating: Good</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Lieberman, 1997	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Before and after study (before and after discharge)</p> <p>Funding: Unfunded</p> <p>Number of centers: 1</p> <p>Outcome assessment: Outcomes were recorded prospectively into a database</p> <p>Number of participants enrolled: 1042 (1042)</p>	<p>Inclusion criteria: THR; received low-dose warfarin prophylaxis</p> <p>Exclusion criteria: Use of anti-inflammatory agent or aspirin; placement of Greenfield filter; use of warfarin for extended period postoperatively</p> <p>Intervention: Patient cohort prior to discharge</p> <p>Comparator: Patient cohort after discharge for 3 months</p>	<p>Duration of followup (d): 90d</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: PE (90d)</p> <p>Intermediate: DVT (90d)</p> <p>Adverse: Major bleeding (90d)</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Partially 3. Sample size calculated? No 4. Adequate description of the cohort? Partially 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Can't tell 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Haas, 1992	<p>Publication type: Full text</p> <p>Geographical location: US</p> <p>Study design: Cohort</p> <p>Funding: Unfunded</p> <p>Number of centers: 1</p> <p>Outcome assessment: NR</p> <p>Number of participants enrolled: 1257 (1257)</p>	<p>Inclusion criteria: Primary TKA; unilateral or bilateral who completed standard surveillance protocol</p> <p>Exclusion criteria: NR</p> <p>Intervention: Patients with DVT were compared to those without DVT to assess the risk of pulmonary embolism</p>	<p>Duration of followup (d): Postoperative</p> <p>Covariates/potential confounders adjusted for: Unadjusted</p> <p>Final: PE (postoperative)</p> <p>Intermediate: DVT, distal DVT, proximal DVT (postoperative)</p> <p>Adverse: NR</p>	<ol style="list-style-type: none"> 1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Partially 3. Sample size calculated? No 4. Adequate description of the cohort? Partially 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Can't tell 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? Yes 9. Completeness of followup? Yes 10. Analysis controls for confounding? No <p>Overall quality rating: Fair</p>

Study, year	Study characteristics	Population, intervention, followup	Followup*, outcomes of interest (timing)	Quality assessment
Lemos, 1991	Publication type: Full text Geographical location: US Study design: Nested Case-control Funding: NR Number of centers: 1 Outcome assessment: Chest roengenogram and VQ scans were performed and confirmed by angiogram Number of participants enrolled: 2348 (240)	Inclusion criteria: Patients undergoing TKA or THA Exclusion criteria: NR Comparisons: Patients with PE after THA or TKA were compared with a matched control of patients without PE for determining risk factors for PE	Duration of followup (d): Postoperative Covariates/potential confounders adjusted for: Gender; procedure Final: PE (postoperative) Intermediate: NR Adverse: NR	1. Unbiased selection of the cohort? Yes 2. Selection minimizes baseline differences in prognostic factors? Partially 3. Sample size calculated? No 4. Adequate description of the cohort? Partially 5. Validated method to ascertain exposure? Yes 6. Validated method for ascertaining clinical outcomes? Yes 7. Outcome assessment blinded to exposure? Can't tell 8. Adequate followup period? No 9. Completeness of followup? Yes 10. Analysis controls for confounding? Partially Overall quality rating: Fair

*Duration of followup is reported as the original study's longest reported followup for outcomes of interest and followup percent is reported for the study's pre-specified primary outcome

† From Happe 2007

Abbreviations: ACS=acute coronary syndrome; AF=atrial fibrillation; ASA=aspirin; CECT=continuous enhanced circulation therapy; d=day(s); DVT=deep vein thrombosis; GI=gastrointestinal; ICD-9=International Classification of Disease, Ninth Revision; ICD-9-CM=International Classification of Disease, Ninth Revision, Clinical Modification; Inc=incorporated; IPC-intermittent pneumatic compression; kg=kilograms; LMWH=low molecular weight heparin; LOS=length of stay; MC=multicenter; mg=milligrams; NOS=not otherwise specified; NR=not reported; PE=pulmonary embolism; PO=by mouth; QD=daily; SQ=subcutaneous; THR=total hip replacement; TKA=total knee arthroplasty; TKR=total knee replacement; UFH=unfractionated heparin; U=units; US=United States; VTE=venous thromboembolism; w=weeks; y=years

Appendix E. Baseline and Procedural Characteristics of Included Trials and Studies

Table 6. Baseline characteristics of patient enrolled in randomized controlled trials evaluating major orthopedic surgery

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari- cosity %	Estro- -gen %	DM %	CA %	CVD %	Prior ortho- pedic sx %
Yokote, 2011	Fondaparinux	84	63.0 (10.0)	83.3	55.0 (10.0)	---	---	0	---	---	---	---	---	---
	Enoxaparin	83	64.0 (11.0)	80.7	55.0 (10.0)	---	---	0	---	---	---	---	---	---
	Placebo	83	63.0 (12.0)	80.7	57.0 (11.0)	---	---	0	---	---	---	---	---	---
Fuji, 2010	Dabigatran 150mg	126	70.9 (7.7)	83.3	59.8 (11.1)	---	---	0	---	---	---	0	---	---
	Dabigatran 220mg	129	72.7 (6.8)	84.5	60.3 (10.7)	---	---	0	---	---	---	0	---	---
	Placebo	124	71.3 (8.5)	84.7	60.8 (11.2)	---	---	0	---	---	---	0	---	---
Chin, 2009	Enoxaparin	110	67 (52-78)*	91.82	---	6.36	---	0	0	---	---	0	---	---
	Control	110	65 (47-77)*	91.81	---	3.64	---	0	0	---	---	0	---	---
Ginsberg, 2009	Dabigatran 150mg QD	871	65.9 (9.5)	58.2	87.6 (20.0)	---	---	---	---	---	---	---	---	---
	Dabigatran 220mg QD	857	66.2 (9.5)	56.7	88.4 (19.1)	---	---	---	---	---	---	---	---	---
	Enoxaparin	868	66.3 (9.6)	58.1	88.0 (19.2)	---	---	---	---	---	---	---	---	---
Edwards, 2008 THA	Enoxaparin + IPC	65	64.2 (31.6-87.7)*	55.4	79.5 (48.6-143.2)*	---	---	0	---	---	---	16.9	---	---
	Enoxaparin	59	67.7 (33.7-86.6)*	59.3	78.8 (40.9-154.6)*	---	---	0	---	---	---	18.6	---	---
Edwards, 2008 TKA	Enoxaparin + IPC	76	68.1 (46.4-87.4)*	63.1	88 (48.2-135.5)*	---	---	0	---	---	---	17.1	---	---
	Enoxaparin	77	68.7 (48.7-88.1)*	55.8	87.7 (53.6-145.5)*	---	---	0	---	---	---	15.6	---	---
Fuji, 2008 THA	Enoxparin 40mg QD	80	60.6 (9.9)	92.5	54.2 (9.8)	12.5	32.5 [†]	---	---	---	---	---	---	---
	Enoxaparin 20mg BID	90	63.0 (9.3)	83.3	54.3 (9.4)	17.8	34.4 [†]	---	---	---	---	---	---	---
	Placebo	86	62.0 (10.3)	87.2	56.0 (10)	16.3	39.5 [†]	---	---	---	---	---	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Fuji, 2008 TKA	Enoxaparin 40mg QD	74	70.0 (9.4)	85.1	57.6 (10.5)	9.5	59.4 [†]	---	---	---	---	---	---	---
	Enoxaparin 20mg BID	84	68.3 (8.7)	94.0	54.0 (8.3)	7.1	41.7 [†]	---	---	---	---	---	---	---
	Placebo	79	68.7 (9.5)	81.0	57.2 (9.5)	13.9	50.6 [†]	---	---	---	---	---	---	---
Thorey, 2008	Early release tourniquet	20	67 (11)	65	83	---	---	0	---	---	---	---	---	---
	Late release tourniquet	20	67 (11)	65	83	---	---	0	---	---	---	---	---	---
Eriksson, 2007a	Dabigatran 150mg QD	703	68 (9)	64	83 (15)	---	---	---	---	---	---	0	0	---
	Dabigatran 220mg QD	679	67 (9)	65	82 (15)	---	---	---	---	---	---	0	0	---
	Enoxaparin	694	68 (9)	69	82 (15)	---	---	---	---	---	---	0	0	---
Eriksson, 2007b	Dabigatran 150mg QD	1163	63 (11)	57	79 (15)	---	---	2	---	---	---	---	---	---
	Dabigatran 220mg QD	1146	65 (10)	56	79 (15)	---	---	3	---	---	---	---	---	---
	Enoxaparin	1154	64 (11)	56	78 (15)	---	---	3	---	---	---	---	---	---
Lassen, 2007	Enoxaparin	152	66.5 (36-88)*	61.8	83.1 (17.6)	---	---	0	---	---	---	0	---	---
	Warfarin	153	66.8 (43-85)*	60.8	83.7 (16)	---	---	0	---	---	---	0	---	---
Bonneux, 2006	Fondaparinux	55	66.9 (8.5)	78.18	---	---	---	---	---	---	---	---	---	---
	Enoxaparin	54	65.7 (10.4)	79.63	---	---	---	---	---	---	---	---	---	---
Senaran, 2006	Enoxaparin	50	55.2 (8.4)	76	---	---	---	---	---	---	---	---	---	---
	Heparin	50	52.4 (11.2)	66	---	---	---	---	---	---	---	---	---	---
Westrich, 2006	Minimum hyperflexed knee	55	68.1 (8.7) [‡]	70.3 [‡]	---	---	---	0	---	---	---	---	---	---
	Standard hyperflexed knee	63			---	---	---	0	---	---	---	---	---	---
Eriksson, 2005	Dabigatran 50mg BID	389	66.1 (31-88)*	57.3	79 (46-125)*	---	---	---	---	---	---	0	0	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
	Dabigatran 150mg BID	390	65.9 (34-89)*	64.6	79 (44-130)*	---	---	---	---	---	---	0	0	---
	Dabigatran 300mg QD	385	66.5 (21-88)*	63.9	79 (43-128)*	---	---	---	---	---	---	0	0	---
	Dabigatran 225mg BID	393	65.9 (33-93)*	58.3	79 (44-130)*	---	---	---	---	---	---	0	0	---
	Enoxaparin	392	65.0 (20-86)*	61.5	79 (47-125)*	---	---	---	---	---	---	0	0	---
Farag, 2005	Epidural Anesthesia	16	63 (8)	81	94 (28)	---	---	---	---	---	---	---	---	---
	Spinal Anesthesia	22	64 (13)	59	100 (26)	---	---	---	---	---	---	---	---	---
Lachiewicz, 2004	IPC (Venaflow)	206	67.3 (23-89)*	62.14	87.7 (50 -146.8)*	---	---	---	---	---	---	---	---	---
	IPC (Kendal)	217	66.4 (30-94)*	66.82	86.6 (45.4-147.7)*	---	---	---	---	---	---	---	---	---
Silbersack, 2004	Enoxaparin + IPC	68	63 (29-90)*	58.82	78 (50-108)*	14.7	---	7.35	66.18	5.88	17.65	5.88	17.65	---
	Enoxaparin + GCS	63	65 (36-87)*	69.84	77 (42-110)*	9.52	---	4.76	61.90	3.17	19.05	3.17	20.63	---
Eriksson, 2003	Extended fondaparinux	327	79 (23-94) [§]	71.9	65 (39-115) [§]	---	7.8	4	---	---	---	---	---	4.9
	Fondaparinux	329	79 (28-96) [§]	70.2	66 (41-127) [§]	---	8.0	3.6	---	---	---	---	---	3.6
Kim, 2003	Cemented	51	54.9 (42-73)* [‡]	46	---	---	---	---	---	---	---	---	---	---
	Non-cemented	51		46	---	---	---	---	---	---	---	---	---	---
Lassen, 2002	Fondaparinux	1140	66 (29-92)*	57	75 (40- 135)*	---	20	4	---	---	---	---	---	10
	Enoxaparin	1133	67 (24-97)*	68	75 (40-145)*	---	24	5	---	---	---	---	---	9
Pitto, 2002	Bone vacuum cement technique	65	73.5 (9.4)	52.3	---	---	---	0	---	---	---	---	---	---
	Standard cement technique	65	71.6 (8.9)	58.5	---	---	---	0	---	---	---	---	---	---
Prandoni, 2002	Extended warfarin	184	68 (48-82)*	54.89	---	---	9.2	---	7.6	1.5	---	2.5	---	---
	Warfarin	176	69 (44-87)*	55.13	---	---	9.7	---	8.5	2.3	---	1.7	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Turpie, 2002	Fondaparinux	1128	67 (18-92) [§]	51	81 (36-169) [§]	---	33	5	---	---	---	---	---	12
	Enoxaparin	1129	67 (19-91) [§]	54	80 (35-226) [§]	---	34	6	---	---	---	---	---	11
Warwick, 2002	Enoxaparin	112	71 (10)	66.96	69 (11)	4.46	---	3.57	6.25	---	---	---	---	---
	VFP	117	73 (9)	63.25	71 (11)	4.27	---	5.98	10.26	---	---	---	---	---
Barden, 2001	Modified position	84	71.2 (54-87)*	71.4	73.4 (43-115)*	---	---	---	---	0	---	0	---	---
	Conventional figure four positioning	76	72.3 (61-84)*	71.0	75.2 (58-118)*	---	---	---	---	0	---	0	---	---
Bauer, 2001	Fondaparinux	517	67.5 (10.7)	60.54	89.0 (20.0)	---	53.3	4.4	---	---	---	---	---	16.8
	Enoxaparin	517	67.5 (10.2)	56.87	88.4 (19.6)	---	53.3	5.4	---	---	---	---	---	14.9
Comp, 2001 THR	Extended enoxaparin	224	64.4 (28-90)*	50.45	81.4 (40.4-149.7)*	---	51.3	---	---	---	---	---	---	---
	Enoxaparin	211	63.4 (26-88)*	49.76	82.7 (40.8-139.3)*	---	55.9	---	---	---	---	---	---	---
Comp, 2001 TKR	Extended enoxaparin	217	66.2 (39-87)*	58.99	88.7 (52.2-147.4)*	---	75.1	---	---	---	---	---	---	---
	Enoxaparin	221	66.3 (34-88)*	55.66	89.2 (45.5-147.4)*	---	73.8	---	---	---	---	---	---	---
Eriksson, 2001	Fondaparinux	831	76.8 (12.3)	77.50	64.3 (13.1)	---	5.4	3.5	---	---	---	9.5	---	4.0
	Enoxaparin	842	77.3 (12.6)	73.40	64.2 (13.8)	---	7.6	3.8	---	---	---	8.8	---	3.1
Fitzgerald, 2001	Warfarin	176	68.2 (9.7)	55.1	84.2	---	---	0	---	---	---	---	---	---
	Enoxaparin	173	67.9 (8.5)	57.2	85.9	---	---	0	---	---	---	---	---	---
Hull, 2000	Dalteparin (preoperative)	496	64 (12)	50	81 (18)	---	---	4.64	16.13	---	---	11.90	---	---
	Dalteparin (postoperative)	487	63 (13)	55.03	80 (19)	---	---	3.49	16.43	---	---	9.45	---	---
	Warfarin	489	63 (13)	50.51	80 (17)	---	---	4.29	13.29	---	---	7.57	---	---
Kennedy, 2000	Aspirin	73	75	50.68	---	---	---	0	0	---	---	0	---	---
	VFP	70	78	54.29	---	---	---	0	0	---	---	0	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Colwell, 1999	Enoxaparin	1516	63.9 (13.17)	55.3	---	---	32.3	---	---	---	---	---	---	---
	Warfarin	1495	64.1 (13.21)	55.9	---	---	27.5	---	---	---	---	---	---	---
Levy, 1999	Fibrin adhesive	29	68.9 (6.3)	79.3	76.7	---	---	---	---	---	---	---	---	---
	No fibrin adhesive	29	70.2 (8.2)	79.3	76.9	---	---	---	---	---	---	---	---	---
Planes, 1999	Enoxaparin	248	64 (11)	55.24	71 (13)	---	---	9	---	---	---	---	---	---
	Tinzaparin	251	65 (11)	56.97	71 (11)	---	---	11	---	---	---	---	---	---
TIFDED Study Group, 1999	Enoxaparin	66	77 (11)	72.73	---	---	---	3.1	---	---	---	3.1	---	---
	Dalteparin	66	76 (10)	78.79	---	---	---	6.1	---	---	---	6.1	---	---
Wakankar, 1999	Tourniquet	37	72.5 (57-85)*	70.2	---	---	---	0	---	---	0	---	---	---
	No tourniquet	40	71.8 (43-91)*	65	---	---	---	0	---	---	0	---	---	---
Kim, 1998	Aspirin	50	---	24.0	---	---	---	---	---	---	---	---	---	---
	Control	50	---	18.0	---	---	---	---	---	---	---	---	---	---
Lassen, 1998	Extended dalteparin	140	68 (30-94)*	52.86	75 (43-125)*	---	---	7.1	15	---	---	2.1	10	---
	Dalteparin	141	70 (28-91)*	56.03	72 (43-105)*	---	---	3.5	18.4	---	---	2.1	10.6	---
Rader, 1998	Heparin	116	68.3 (11)	78.45	74 (19)	12.07	---	11.21	---	2.59	5.18	0	---	---
	Enoxaparin	130	69.6 (13)	62.31	78 (12)	10.00	---	4.64	---	0.77	6.15	0	---	---
Ryan, 1998	IPC	50	70.1	62	71.5	---	---	---	---	---	---	---	---	---
	GCS	50	67.5	62	73.4	---	---	---	---	---	---	---	---	---
Warwick, 1998	Enoxaparin	143	68 (11)	39.16	71 (10)	---	---	2	---	---	---	---	---	---
	VFP	147	68 (11)	36.05	71 (12)	---	---	1	---	---	---	---	---	---
Andersen, 1997	Extended dalteparin	20	67 (52-84)*	40	76 (50-104)*	---	---	---	---	---	---	---	---	---
	Dalteparin	21	67 (34-84)*	48	73 (52-94)*	---	---	---	---	---	---	---	---	---
Dahl, 1997	Extended dalteparin	117	70.9	68.4	73.2	---	---	8.5	---	---	---	9.4	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
	Dalteparin	110	71.4	73.6	71.6	---	---	4.5	---	---	---	9.1	---	---
Eriksson, 1997a	Desirudin	225	68.6 (9.3)	58	74.8 (12.3)	19	37	4	20	---	---	3	0.89	16
	UFH	220	68.2 (9.8)	58	73.7 (13.2)	18	32	2	16	---	---	3	5	15
Eriksson, 1997b	Desirudin	1043	66 (27-90) [§]	56.6	73 (42-120) [§]	15.1	41.0	6.5	---	---	---	12.3	---	---
	Enoxaparin	1036	67 (18-87) [§]	60.0	74 (43-128) [§]	18.0	41.6	6.0	---	---	---	12.4	---	---
Francis, 1997	Dalteparin	271	63 (13)	53.14	80 (19)	---	---	9.59	---	---	---	---	---	---
	Warfarin	279	63 (14)	52.69	80 (18)	---	---	8.96	---	---	---	---	---	---
Nilsson, 1997	Extended enoxaparin	131	70 (44-87)*	57.25	---	---	---	6	21	---	---	---	---	---
	Enoxaparin	131	70 (44-87)*	56.49	---	---	---	9	24	---	---	---	---	---
Planes, 1997	Extended enoxaparin	90	70 (9.1)	47.78	---	---	---	2.22	14.44	---	---	---	---	13.33 [†]
	Enoxaparin	89	68 (8.2)	38.2	---	---	---	1.12	14.61	---	---	---	---	10.11
Samama, 1997	Enoxaparin	85	67.2 (31.6-9.21) [§]	31.8	74.4 (12.1)	---	---	0	---	---	---	---	---	---
	Placebo	85	67.2 (31.6-87.5) [§]	51.8	71.4 (11.1)	---	---	0	---	---	---	---	---	---
Eriksson, 1996	Desirudin	277	66.6 (9.7)	60.3	73.1 (12.6)	16.7	39.4	3.6	18.1	---	---	4.3	7.9	18.1
	UFH	277	66.7 (9.8)	64.3	72.9 (13.9)	18.8	35.4	4.7	18.4	---	---	2.5	4.7	14.1
Kalodiki, 1996	Enoxaparin + GCS	32	69 (54-85)*	40.63	---	---	34.38	0	46.88	---	---	3.12	---	---
	Enoxaparin	32	67(53-82)*	59.38	---	---	34.38	3.13	43.75	---	---	3.13	---	---
	Placebo	14	72 (60-83)*	57.14	---	---	21.43	7.14	28.57	---	---	7.14	---	---
Laupacis, 1996	Cemented	124	63.9 (7.6)	48.4	---	---	---	3.2	---	---	---	---	---	---
	Non-cemented	126	63.9 (7.4)	46	---	---	---	4.8	---	---	---	---	---	---
Leclerc, 1996	Warfarin	334	69.2 (9.2)	63.2	78.2 (15.9)	---	---	10.2	---	---	---	---	---	---
	Enoxaparin	336	68.0 (9.4)	63.1	79.2 (16.0)	---	---	9.5	---	---	---	---	---	---
Lotke, 1996	Aspirin	166	66.4	61.2 [†]	---	---	---	---	---	---	---	---	---	---
	Warfarin	136	67.1	---	---	---	---	---	---	---	---	---	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Schwartz-mann, 1996	Enoxaparin	52	62 (10)	58	69 (12)	3.8	15.4	0	3.8	0	---	0	---	---
	UFH	47	58 (11)	60	69 (12)	4.2	23.4	0	2.1	0	---	0	---	---
Stannard, 1996	UFH then ASA + VFP	25	65.0 (51-79)*	---	---	---	---	---	---	---	---	---	---	---
	UFH then aspirin	25	69.7 (28-86)*	---	---	---	---	---	---	---	---	---	---	---
	VFP	25	68.7 (48-86) *	---	---	---	---	---	---	---	---	---	---	---
Stone, 1996	Enoxaparin	25	64 (37-82)*	68	67 (41-92)*	---	---	0	---	---	---	0	---	---
	IPC	25	64 (42-83)*	60	69 (48-90)*	---	---	0	---	---	---	0	---	---
Westrich, 1996	Aspirin + VFP	61	---	67.12 [‡]	---	---	---	0	---	---	---	---	---	---
	Aspirin	61	---	---	---	---	---	0	---	---	---	---	---	---
Williams-Russo, 1996	General Anesthesia	81	68 (9)	65	---	---	38	10	---	---	---	---	---	---
	Regional Anesthesia	97	68 (8)	74	---	---	33	3	---	---	---	---	---	---
Abdel-Salam, 1995	Tourniquet	40	72 (65-80)*	57.5	---	---	---	---	---	---	0	---	---	---
	No tourniquet	40	74 (64-82)*	62.5	---	---	---	---	---	---	0	---	---	---
Avikainen, 1995	Enoxaparin	83	65 (27-86)*	63.86	72 (39-110)*	---	---	2.41 [#] 0**	9.64	---	---	---	---	30.12
	UFH	84	66 (34-86)*	70.24	71 (36-126)*	---	---	3.57 [#] 2.38**	7.14	---	---	---	---	27.38
Colwell, 1995	Enoxaparin	228	67.5 (9.5)	53.1	86.9 (17.9)	---	---	0	---	---	---	---	---	---
	Heparin	225	68.6 (8.8)	59.6	84.8 (17.3)	---	---	0	---	---	---	---	---	---
Warwick, 1995	Enoxaparin	78	---	---	---	---	---	---	---	---	---	---	---	---
	Control	78	---	---	---	---	---	---	---	---	---	---	---	---
Colwell, 1994	Enoxaparin 30mg Q12h	195	65.6 (10.97)	49.74	78.4 (17.12)	---	---	0	---	---	---	---	---	---
	Enoxaparin 40mg QD	203	65.0 (11.31)	51.23	78.8 (17.84)	---	---	0	---	---	---	---	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Fauno, 1994	UFH	209	65.6 (10.65)	51.67	78.2 (15.96)	---	---	0	---	---	---	---	---	---
	Enoxaprain	92	71 (11)	61.96	78 (14)	---	---	0	23.91	---	---	---	---	---
	UFH	93	70 (10)	59.14	72 (14)	---	---	0	19.35	---	---	---	---	---
Lieberman, 1994	Aspirin + IPC	113	67 (40-87)*	59.29	75 (45-100)*	---	---	0	---	---	---	---	---	---
	Aspirin	118	66 (40-80)*	55.93	75 (48-106)*	---	---	0	---	---	---	---	---	---
Menzin, 1994	UFH	209	65.7 (10.7)	52	---	---	---	0	---	---	16	---	---	---
	Enoxaparin 40mg QD	202	65.0 (11.3)	51	---	---	---	0	---	---	20	---	---	---
	Enoxaparin 30mg Q12h	192	65.8 (11.0)	49	---	---	---	0	---	---	14	---	---	---
Santori, 1994	Heparin	65	69.8 (6.22)	76.92	---	---	---	0	0	---	---	0	---	---
	VFP	67	72.4 (6.65)	71.64	---	---	---	0	0	---	---	0	---	---
Hull, 1993	Tinzaparin	715	66 (12)	56.08	---	---	---	0	---	---	8.67	8.67	2.80	---
	Warfarin	721	66 (12)	61.44	---	---	---	0	---	---	7.63	8.60	4.88	---
Fordyce, 1992	VFP	39	68.1	61.54	69.75	---	---	0	41.03	---	---	---	---	---
	Control	40	71.2	62.5	69.9	---	---	0	55.00	---	---	---	---	---
Francis, 1992	Warfarin	103	64 (12)	49.51	---	---	---	5.83	---	---	---	---	---	---
	IPC	98	64 (12)	56.12	---	---	---	7.14	---	---	---	---	---	---
Jorgensen, 1992	Dalteparin	30	79 (57-95) [§]	70.0	---	---	---	10.0	---	---	---	0	---	---
	Placebo	38	80 (61-90) [§]	81.6	---	---	---	0	---	---	---	9	---	---
Wilson, 1992	VFP	28	71.1 (6.7)	82.14	---	---	---	---	---	---	---	---	---	---
	Control	31	70.1 (6.8)	67.74	---	---	---	---	---	---	---	---	---	---
Bailey, 1991	Warfarin	45	64.4 (45-80)*	51	81.3 (35.7-120)*	---	---	---	---	---	---	---	---	---
	IPC	50	65.3 (41-88)*	52	72.2 (42-109)*	---	---	---	---	---	---	---	---	---
Eriksson, 1991	Dalteparin	67	68.4 (8.2)	59.70	---	20.89	---	10.45	28.36	2.99	10.45	---	4.48	52.24

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
	UFH	69	69.0 (8.0)	56.52	---	14.49	---	14.49	33.33	0	2.90	---	5.80	47.83
Jorgensen, 1991	General Anesthesia	22	64 (38-85)*	68.1	---	---	---	0	13.6	---	---	---	---	---
	Epidural Anesthesia	17	70.5 (52-87)*	76.5	---	---	---	0	11.8	---	---	---	---	---
Lassen, 1991	Tinzaparin	93	67 (40-85) [§]	51.6	73 (40-101) [§]	---	---	6.5	34.4	---	---	3.2	---	---
	Placebo	97	67 (40-86) [§]	51.5	74 (48-126) [§]	---	---	6.2	28.9	---	---	4.1	---	---
Levine, 1991	Enoxaparin	333	66.2 (10.39)	56.5	---	---	---	9.61	---	---	---	---	---	39.34
	UFH	332	66.8 (9.09)	51.8	---	---	---	10.84	---	---	---	---	---	42.47
Mitchell, 1991	General Anesthesia	38	64 (38-84)* [‡]	37.5 [‡]	---	---	---	---	---	---	---	---	---	---
	Epidural Anesthesia	34			---	---	---	---	---	---	---	---	---	---
Planes, 1991	General Anesthesia + Enoxaparin	62	66.1 (1)	54.8	68.9 (1.5)	---	32.3	9.7	43.6	---	---	4.8	---	---
	Epidural Anesthesia + Enoxaparin	61	66.8 (1.1)	47.5	70.8 (1.3)	---	41.0	4.9	39.3	---	---	1.6	---	---
	Epidural Anesthesia alone	65	66.7 (1.2)	55.6	68.7 (1.6)	---	33.9	7.7	44.6	---	---	0	---	---
Torholm, 1991	Dalteparin	58	67 (43-85) [§]	60.3	---	---	---	8.6	---	---	---	0	---	---
	Placebo	54	64 (43-81) [§]	50.0	---	---	---	9.3	---	---	---	1.9	---	---
Woolson, 1991	Aspirin + IPC	70	62.3	50 ^{††}	74	---	---	6 ^{††}	7 ^{††}	---	---	---	---	---
	Warfarin + IPC	69	67.6	55 ^{††}	75	---	---	14 ^{#††}	13 ^{††}	---	---	---	---	---
	IPC	73	66.3	63	71	---	---	7 ^{#††}	8 ^{††}	---	---	---	---	---
Haas, 1990 Unilateral	Aspirin	36	70.2	69.44	---	5.56	58.33	8.33	25.00	---	8.33	---	19.44	---
	IPC	36	67.7	72.22	---	13.89	50.00	5.56	19.44	---	8.33	---	13.89	---
Haas, 1990 Bilateral	Aspirin	22	71.1	68.18	---	0	59.09	0	18.18	---	0	---	18.18	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
	IPC	25	69.9	52.00	---	28.00	52.00	4.00	16.00	---	12.00	---	16.00	---
Sorensen, 1990	Tinzaparin	31	---	64.42 ⁺	---	---	---	---	---	---	---	---	---	---
	Placebo	33	---	---	---	---	---	---	---	---	---	---	---	---
Dechav-anne, 1989	Dalteparin 2500U Q12h	41	65.1 (10.8)	60.98	66.5 (11.3)	---	---	7.32	36.59	---	---	0	---	48.78
	Dalteparin 5000U QD	41	62.8 (10.6)	53.66	70.8 (13.6)	---	---	4.88	36.59	---	---	2.44	---	36.59
	Heparin	40	62.8 (10.6)	50	70.0 (12.9)	---	---	12.5	42.5	---	---	7.5	---	45
Monreal, 1989	Dalteparin	46	75.73 (9.86)	80.43	---	---	---	---	---	---	---	4.35	---	---
	Heparin	44	78.31(12.1)	84.09	---	---	---	---	---	---	---	2.27	---	---
Powers, 1989	Warfarin	65	74.5 (43-90)*	64.62	---	---	---	6.15	---	---	---	---	---	---
	Aspirin	66	73.0 (48-87)*	71.21	---	---	---	4.55	---	---	---	---	---	---
	Placebo	63	76.6 (30-91)*	80.95	---	---	---	6.35	---	---	---	---	---	---
Planes, 1988	Enoxaparin	124	65.4 (9.1)	50.81	69.1 (13.4)	---	34.68	---	25	0.81	---	---	---	35.48
	Heparin	113	66.3 (12.5)	59.3	65.3 (12.5)	---	23.89	---	29.20	0.88	---	---	---	29.20
Barre, 1987	Dalteparin	40	63.1	62.5	69.2	---	---	7.5	45	---	---	0	---	---
	Heparin	40	63.3	45	73.3	---	---	7.5	55	---	---	5.0	---	---
Palement, 1987	Warfarin	72	---	---	---	---	---	---	---	---	---	---	---	---
	IPC	66	---	---	---	---	---	---	---	---	---	---	---	---
Alfaro, 1986	Aspirin 250 mg/d	30	66.06 (8.93)	43.3	---	---	---	6.7	33.3	---	---	0	13.3	16.7
	Aspirin 1 g/d	30	62.04(10.99)	50.0	---	---	---	3.3	36.7	---	---	0	6.7	10.0
	Control	30	61.99 (7.17)	36.7	---	---	---	0	33.3	---	---	0	16.7	13.3
Turpie, 1986	Enoxaparin	50	66.82 (9.55)	44.0	---	---	---	10.0	---	---	---	0	---	22.0
	Placebo	50	67.3 (8.85)	60.0	---	---	---	10.0	---	---	---	0	---	18.0
McKenzie, 1985	General Anesthesia	20	72.3 (3.8)	70	---	---	---	---	---	---	---	---	---	---
	Spinal Anesthesia	20	73.9 (4.1)	80	---	---	---	---	---	---	---	---	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Vari-cosity %	Estro-gen %	DM %	CA %	CVD %	Prior ortho-pedic sx %
Welin-Berger, 1982	Heparin	20	66.8 (8.3)	71.7 [†]	---	---	---	---	---	---	---	---	---	---
	Control	20	65.7 (10.6)		---	---	---	---	---	---	---	---	---	---
Modig, 1981	General Anesthesia	15	65.4 (6.3)	53.3	---	---	---	0	0	---	0	---	0	---
	Epidural Anesthesia	15	66.5 (5.5)	46.7	---	---	---	0	0	---	0	---	0	---
McKenna, 1980	Aspirin	9	72	100	---	---	0	0	---	0	---	0	---	---
	Placebo	12	66	81.82	---	---	0	0	---	0	---	0	---	---

*Mean (range)

†BMI>25

‡Value for the total study population

§Median (range)

||BMI≥30

¶Conversion or revision of total hip replacement

patients with history of DVT

**patients with history of PE

††Percent of hips

Abbreviations: ASA=aspirin; BID=twice daily; CA=cancer; CVD=cardiovascular disease; DM=diabetes mellitus; d=day; GCS=graduated compression stocking; HFS=hip fracture surgery; g=gram; hx=history; IPC=intermittent pneumatic compression; kg=kilograms; mg=milligram; N=total number of patients; QD=daily; SD=standard deviation; sx=surgery; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VFP=venous foot pump; VTE=venous thromboembolism; Wt=weight

Table 7. Procedural characteristics of randomized controlled trials evaluating patients who had major orthopedic surgery.

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Yokote, 2011	Fondaparinux	84	100	0	AL: 100	---	---	GA: 100	---
	Enoxaparin	83	100	0	AL: 100	---	---	GA: 100	---
	Placebo	83	100	0	AL: 100	---	---	GA: 100	---
Fuji, 2010	Dabigatran 150mg	126	100	---	---	109.2 (44.2)	---	GA: 77.0 Non-GA: 23.0	---
	Dabigatran 220mg	129	100	---	---	108.9 (44.2)	---	GA: 74.4 Non-GA: 25.6	---
	Placebo	124	100	---	---	108.8 (46.9)	---	GA: 74.2 Non-GA: 25.8	---
Chin, 2009	Enoxaparin	110	---	---	---	93.0 (55-155)*	---	GA: 58.18 RA: 41.82	8.1 (4-19)*
	Control	110	---	---	---	94.2 (45-195)*	---	GA: 57.27 RA: 42.73	7.9 (4-24)*
Ginsberg, 2009	Dabigatran 150mg QD	871	100	---	---	91 (30)	---	GA: 54.0 RA: 45.8	---
	Dabigatran 220mg QD	857	100	---	---	91 (28)	---	GA: 52.9 RA: 46.3	---
	Enoxaparin	868	100	---	---	90 (28)	---	GA: 51.7 RA: 47.5	---
Edwards, 2008 THA	Enoxaparin + IPC	65	---	---	---	---	---	---	3.0
	Enoxaparin	59	---	---	---	---	---	---	3.13
Edwards, 2008 TKA	Enoxaparin + IPC	76	---	---	---	---	---	---	3.1
	Enoxaparin	77	---	---	---	---	---	---	3.3
Fuji, 2008 THA	Enoxaparin 40mg QD	80	100	43.8	---	123.6 (39)	---	GA: 16.3 RA: 0	---
	Enoxaparin 20mg BID	90	100	46.7	---	123 (39.6)	---	GA: 21.1 RA: 0	---
	Placebo	86	100	40.7	---	129 (46.8)	---	GA: 16.3 RA: 0	---
Fuji, 2008 TKA	Enoxaparin 40mg QD	74	100	77.0	---	132 (46.8)	---	GA: 18.9 RA: 0	---
	Enoxaparin 20mg BID	84	100	84.5	---	127.2 (37.2)	---	GA: 21.4 RA: 0	---
	Placebo	79	100	78.5	---	126.6 (39)	---	GA: 12.7 RA: 0	---
Thorey, 2008	Early release tourniquet	20	---	100	---	58 (18)	---	GA: 100	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Eriksson, 2007a	Late release tourniquet	20	---	100	---	51 (17)	---	GA: 100	---
	Dabigatran 150mg QD	703	100	---	---	91 (30)	---	GA: 24 RA: 47 GA+RA: 29	---
	Dabigatran 220mg QD	679	100	---	---	91 (28)	---	GA: 22 RA: 49 GA+RA: 29	---
	Enoxaparin	694	100	---	---	90 (28)	---	GA: 22 RA: 48 GA+RA: 30	---
Eriksson, 2007b	Dabigatran 150mg QD	1163	100	---	---	85 (29)	---	GA: 24 RA: 66 GA+RA: 10	9 (7-12) [†]
	Dabigatran 220mg QD	1146	100	---	---	85 (29)	---	GA: 26 RA: 66 GA+RA: 8	9 (7-12) [†]
	Enoxaparin	1154	100	---	---	87 (29)	---	GA: 24 RA: 68 GA+RA: 8	9 (7-12) [†]
Lassen, 2007	Enoxaparin	152	---	---		96 (42-199.8)*	---	GA: 30.2 RA: 54.4	6 (2-24)*
	Warfarin	153	---	---		96.6 (40.2- 250.2)*	---	GA: 35.8 RA: 50.3	6 (3-38)*
Bonneux, 2006	Fondaparinux	55	96.36	---	---	---	---	GA+RA:100	---
	Enoxaparin	54	92.59	---	---	---	---	GA+RA:100	---
Senaran, 2006	Enoxaparin	50	---	---	---	---	---	GA: 100	---
	Heparin	50	---	---	---	---	---	GA: 100	---
Westrich, 2006	Minimum hyperflexed knee	55	100	100	---	---	---	RA: 100	---
	Standard hyperflexed knee	63	100	100	---	---	---	RA: 100	---
Eriksson, 2005	Dabigatran 50mg BID	389	100	---	---	84 (30-234)*	---	GA: 26.3 RA:73.7	---
	Dabigatran 150mg BID	390	100	---	---	90 (30-324)*	---	GA: 27.3 RA: 72.7	---
	Dabigatran 300mg QD	385	100	---	---	84 (30-234)*	---	GA: 25.8 RA: 74.2	---
	Dabigatran 225mg BID	393	100	---	---	84 (30-216)*	---	GA: 27.5 RA: 72.5	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	Enoxaparin	392	100	---	---	90 (24-276)*	---	GA: 27.9 RA: 72.1	---
Farag, 2005	Epidural Anesthesia	16	---	---	---	---	---	RA: 100	---
	Spinal Anesthesia	22	---	---	---	---	---	RA: 100	---
Lachiewicz, 2004	IPC (Venaflow)	206	86.89	---	---	---	---	GA: 14.56 RA: 84.95 GA+RA: 0.49	---
	IPC (Kendal)	217	82.95	---	---	---	---	GA: 11.98 RA: 87.56 GA+RA: 0.46	---
Silbersack, 2004	Enoxaparin + IPC	68	100	42.65	---	89 (55-177)*	133 (80-195)*	GA: 27.94 RA: 72.06	---
	Enoxaparin + GCS	63	100	46.03	---	93 (46-159)*	137 (70-210)*	GA: 26.98 RA: 73.02	---
Eriksson, 2003	Extended fondaparinux	327	---	23.9	---	99 (27-335)*	---	GA: 31.2 RA: 67.6 GA+RA: 1.2	---
	Fondaparinux	329	---	25.2	---	95 (27-255)*	---	GA: 31.0 RA: 67.5 GA+RA: 1.5	---
Kim, 2003	Cemented	51	---	50	---	---	---	---	---
	Non-cemented	51	---	---	---	---	---	---	---
Lassen, 2002	Fondaparinux	1140	89	60	---	138 (48)	---	GA: 35 RA: 61 GA+RA: 5	---
	Enoxaparin	1133	87	60	---	144 (52.2)	---	GA: 38 RA: 57 GA+RA: 4	---
Pitto, 2002	Bone vacuum cement technique	65	100	100	DL: 100	75 (8)	---	GA: 100	11.5 (2)
	Standard cement technique	65	100	100	DL: 100	71 (11)	---	GA: 100	12 (2.5)
Prandoni, 2002	Extended warfarin	184	---	---	---	---	---	GA: 97.0	9 (5-18)*
	Warfarin	176	---	---	---	---	---	GA: 97.2	9 (4-20)*

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Turpie, 2002	Fondaparinux	1128	84	51	---	148.8 (57)	---	GA: 70 RA: 26 GA+RA: 4	---
	Enoxaparin	1129	87	53	---	147 (57)	---	GA: 72 RA: 23 GA+RA: 5	---
Warwick, 2002	Enoxaparin	112	100	---	---	---	---	RA: 83	---
	VFP	117	100	---	---	---	---	RA: 86	---
Barden, 2001	Modified position	84	100	100	AL: 100	---	---	---	---
	Conventional figure four positioning	76	100	100	AL: 100	---	---	---	---
Bauer, 2001	Fondaparinux	517	92.5	93.2	---	127 (39)	---	GA: 74.7 RA: 24.4 GA+RA: 1.0	---
	Enoxaparin	517	92.6	93.6	---	128 (42)	---	GA: 71.4 RA: 27.5 GA+RA: 1.2	---
Comp, 2001 THR	Extended enoxaparin	224	78.6	---	---	---	---	GA: 75.0 RA: 25.0	---
	Enoxaparin	211	78.2	---	---	---	---	GA: 69.7 RA: 30.3	---
Comp, 2001 TKR	Extended enoxaparin	217	72.4	---	---	---	---	GA: 67.7 RA: 32.3	---
	Enoxaparin	221	76.0	---	---	---	---	GA: 67.9 RA: 32.1	---
Eriksson, 2001	Fondaparinux	831	---	21.2	---	101 (39)	---	GA: 31.5 RA: 66.7 GA+RA: 1.8	---
	Enoxaparin	842	---	21.8	---	104 (44)	---	GA: 32.8 RA: 65.2 GA+RA: 2.0	---
Fitzgerald, 2001	Warfarin	176	100	92.0	---	121.2 (55.8)	---	GA: 61.9 RA: 38.1	---
	Enoxaparin	173	100	91.3	---	119.4 (44.4)	---	GA: 64.7 RA: 35.3	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Hull, 2000	Dalteparin (preoperative)	496	81.85	22.58	---	---	---	---	---
	Dalteparin (postoperative)	487	81.52	25.05	---	---	---	---	---
	Warfarin	489	85.89	22.49	---	---	---	---	---
Kennedy, 2000	Aspirin	73	---	100	---	64	---	GA: 45.21 RA: 54.79	---
	VFP	70	---	100	---	59	---	GA: 60 RA: 41.43	---
Colwell, 1999	Enoxaparin	1516	100	---	---	---	---	---	---
	Warfarin	1495	100	---	---	---	---	---	---
Levy, 1999	Fibrin adhesive	29	---	100	---	---	---	---	---
	No fibrin adhesive	29	---	100	---	---	---	---	---
Planes, 1999	Enoxaparin	248	100	---	---	89 (44)	161 (56)	---	---
	Tinzaparin	251	100	---	---	87 (39)	159 (61)	---	---
TIFDED Study Group, 1999	Enoxaparin	66	---	---	---	69 (33)	---	---	---
	Dalteparin	66	---	---	---	70 (26)	---	---	---
Wakankar, 1999	Tourniquet	37	---	100	---	---	---	GA: 100	---
	No tourniquet	40	---	100	---	---	---	GA: 100	---
Kim, 1998	Aspirin	50	100	0	Modified Gibson: 100	---	---	GA: 100	---
	Control	50	100	0	Modified Gibson: 100	---	---	GA: 100	---
Lassen, 1998	Extended dalteparin	140	88.2 ⁺	61.43	PL: 100	110 (55-280)*	---	GA: 37.14 RA: 62.86	---
	Dalteparin	141		67.38	PL: 100	105 (50-275)*	---	GA: 38.30 RA: 61.70	---
Rader, 1998	Heparin	116	100	---	THA L: 100 TKA AM: 100	THA: 72(14) TKA: 86(18)	---	GA:45.69 RA:54.31	16.4 (13-21)* ⁺
	Enoxaparin	130	100	---	THA L:100 TKA AM: 100	THA:74(17) TKA: 88(15)	---	GA:40.77 RA:59.23	
Ryan, 1998	IPC	50	100	---	---	---	---	RA: 100	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	GCS	50	100	---	---	---	---	RA: 100	---
Warwick, 1998	Enoxaparin	143	100	64.34	P: 61	---	---	RA: 87	---
	VFP	147	100	66.67	P: 56	---	---	RA: 84	---
Andersen, 1997	Extended dalteparin	20	---	35	---	99 (60-140)*	149 (120-180)*	---	---
	Dalteparin	21	---	43	---	105 (60-180)*	165 (120-270)*	---	---
Dahl, 1997	Extended dalteparin	117	92.5 [†]	79.1	---	107	---	GA: 0.88 [†] RA: 99.12 [‡]	---
	Dalteparin	110		84.1	---	107	---		---
Eriksson, 1997a	Desirudin	225	100	81	---	101 (30)	---	GA:5 RA: 88 GA+RA: 6	---
	UFH	220	100	75	---	104 (30)	---	GA:6 RA: 86 GA+RA: 9	---
Eriksson, 1997b	Desirudin	1043	100	44.6	---	82.0 (22-297) [†]	---	RA: 55.7	---
	Enoxaparin	1036	100	44.3	---	80.0 (25-345) [†]	---	RA: 55.8	---
Francis, 1997	Dalteparin	271	76.38	29.52	---	161 (72)	221 (75)	GA:67.53 RA:32.47	---
	Warfarin	279	69.53	29.75	---	163 (62)	225 (67)	GA:63.44 RA:36.56	---
Nilsson, 1997	Extended enoxaparin	131	100	---	L:100	102 (66-312)*	---	GA: 3.8 RA: 86.3 GA+RA: 9.9	---
	Enoxaparin	131	100	---	L: 100	114 (60-300)*	---	GA: 6.1 RA: 84.0 GA+RA: 9.9	---
Planes, 1997	Extended enoxaparin	90	---	---	AL: 6.36 [†] PL: 93.64 [‡]	---	127.67 (19.95)	GA: 58.38 [†] RA: 41.62 [‡]	---
	Enoxaparin	89	---	---		---	125.83 (19.77)		---
Samama, 1997	Enoxaparin	85	100	74.1	A: 24.7 P: 71.8	70.1 (27.3)	---	RA: 100	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	Placebo	85	100	67.1	A: 21.2 P: 71.6	69.2 (27.9)	---	RA: 100	---
Eriksson, 1996	Desirudin	277	100	67.7	---	---	---	RA: 51.5	---
	UFH	277	100	67.5	---	---	---	RA: 51.6	---
Kalodiki, 1996	Enoxaparin + GCS	32	100	0	---	98 (50-185)*	---	GA: 100	---
	Enoxaparin	32	100	0	---	98 (45-215)*	---	GA: 100	---
	Placebo	14	100	0	---	96 (60-135)*	---	GA: 100	---
Laupacis, 1996	Cemented	124	100	100	DL: 100	---	---	GA: 85.5 RA: 14.5	---
	Non-cemented	126	100	100	DL: 100	---	---	GA: 90.5 RA: 9.5	---
Leclerc, 1996	Warfarin	334	93.4	89.2	---	124.3 (38.5)	---	GA:85.9 RA:14.1	---
	Enoxaparin	336	92.3	89.0	---	126.2 (44.7)	---	GA:87.2 RA:12.8	---
Lotke, 1996	Aspirin	166	---	---	---	---	---	---	---
	Warfarin	136	---	---	---	---	---	---	---
Schwartzmann, 1996	Enoxaparin	52	100	62	AL: 100	90.8	---	RA: 100	---
	UFH	47	100	47	AL: 100	93.6	---	GA: 2 RA: 97.87 GA+RA: 0	---
Stannard, 1996	UFH then aspirin + VFP	25	88.0	0	P: 100	106 (85-128)*	---	GA: 16.0 RA: 84.0	---
	UFH then aspirin	25	100	0	P: 100	111 (87-140)*	---	GA: 12.0 RA: 88.0	---
	VFP	25	92.0	0	P: 100	113 (91-135)*	---	GA: 20.0 RA: 80.0	---
Stone, 1996	Enoxaparin	25	100	100	P: 100	---	---	---	---
	IPC	25	100	100	P: 100	---	---	---	---
Westrich, 1996	Aspirin + VFP	61	100	100	---	---	---	RA: 100	---
	Aspirin	61	100	100	---	---	---	RA: 100	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Abdel-Salam, 1995	Tourniquet	40	100	100	---	60-105 ^s	---	GA: 100	12 (9-20)*
	No tourniquet	40	100	100	---	60-95 ^s	---	GA: 100	12 (8-19)*
Avikainen, 1995	Enoxaparin	83	---	42.17	---	---	---	GA:29.69 RA:78.31	---
	UFH	84	---	30.95	---	---	---	GA:1.19 RA: 72.62	---
Colwell, 1995	Enoxaparin	228	---	---	---	---	---	---	---
	Heparin	225	---	---	---	---	---	---	---
Warwick, 1995	Enoxaparin	78	100	---	---	---	---	---	---
	Control	78	100	---	---	---	---	---	---
Williams-Russo, 1996	General Anesthesia	81	100	100	---	88 (32)	---	GA: 100	12.7 (4.3)
	Regional Anesthesia	97	100	100	---	85 (33)	---	RA: 100	12.1 (4.5)
Colwell, 1994	Enoxaparin 30mg Q12h	195	86	23	---	---	---	GA:66 RA:33	---
	Enoxaparin 40mg QD	203	83	27	---	---	---	GA:63 RA:35	---
	UFH	209	87	29	---	---	---	GA:65 RA:34	---
Fauno, 1994	Enoxaparin	92	100	65.22	---	104 (20)	---	GA: 10.87	---
	UFH	93	100	62.37	---	102 (24)	---	GA: 19.35	---
Leiberman, 1994	Aspirin + IPC	113	100	17.74 ^{ll}	PL: 100	86	---	Hypotensive regional: 100	---
	Aspirin	118	100	13.49 ^{ll}	PL: 100	87	---	Hypotensive regional: 100	---
Menzin, 1994	UFH	209	---	---	---	162 (78)	---	---	11.3
	Enoxaparin 40mg QD	202	---	---	---	156 (84)	---	---	9.9
	Enoxaparin 30mg Q12h	192	---	---	---	150 (66)	---	---	9.5
Santori, 1994	Heparin	65	100	---	DL: 100	65 (9.89)	---	GA: 100	---
	VFP	67	100	---	DL: 100	70 (11.98)	---	GA: 100	---
Hull, 1993	Tinzaparin	715	84.62	54.13	---	---	128 (52)	GA:53.85 RA: 20.97 GA+RA: 25.17	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	Warfarin	721	84.47	57.98	---	---	127 (48)	GA:53.81 RA: 20.94 GA+RA: 25.24	---
Fordyce, 1992	VFP	39	100	100	DL: 12.82 P: 87.18	---	104.5	GA: 7.69	---
	Control	40	100	100	DL: 17.50 P: 82.50	---	112.6	GA: 15.00	---
Francis, 1992	Warfarin	103	100	24.53	AL: 100	---	198 (36)	GA: 69.90 RA: 30.10	9 [†]
	EPC	98	100	25.51	AL: 100	---	205 (40)	GA: 61.22 RA: 38.78	
Jorgensen, 1992	Dalteparin	30	---	---	---	57 (25 -115) [†]		GA: 66.67 RA: 30	14 (2-117) [†]
	Placebo	38	---	---	---	60 (35-105) [†]		GA: 53 RA: 45	16 (3-50) [†]
Wilson, 1992	VFP	28	---	---	---	139.2 (34.9)	---	---	---
	Control	31	---	---	---	132.1 (32.4)	---	---	---
Bailey, 1991	Warfarin	45	57.8	80.9	L:100	---	---	GA: 82.2 RA:6.7	---
	IPC	50	54	75.5	L:100	---	---	GA: 80 RA:14	---
Eriksson,1991	Dalteparin	67	---	79.10	AL: 100	123 (22)	---	GA: 14.93 RA:85.07	---
	UFH	69	---	79.71	AL: 100	124 (29)	---	GA: 7.25 RA:92.75	---
Jorgensen, 1991	General Anesthesia	22	---	---	---	---	---	GA: 100	---
	Epidural Anesthesia	17	---	---	---	---	---	RA: 100	---
Lassen, 1991	Tinzaparin	93	100	65.6	PL: 100	117 (55-200) [†]	---	GA: 72.0 RA: 28.0	---
	Placebo	97	100	71.1	PL: 100	123 (50-250) [†]	---	GA: 69.1 RA: 30.9	---
Levine, 1991	Enoxaparin	333	---	38.74	---	166 (56.6)	---	---	---
	UFH	332	---	39.16	---	172 (67.7)	---	---	---
Mitchell, 1991	General Anesthesia	38	100	76.4	---	121	---	GA: 100	11

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Planes, 1991	Epidural Anesthesia	34	100	---	---	122	---	RA: 100	10.4
	General Anesthesia + Enoxaparin	62	100	---	PL: 100	73.7 (2.4)	---	GA: 100	---
	Epidural Anesthesia + Enoxaparin	61	100	---	PL: 100	73.3 (2.3)	---	RA: 100	---
	Epidural Anesthesia alone	65	100	---	PL: 100	74.9 (1.7)	---	RA: 100	---
Torholm, 1991	Dalteparin	58	76	---	---	---	---	GA: 88 RA: 12	---
	Placebo	54	80	---	---	---	---	GA: 81 RA: 19	---
Woolson, 1991	Aspirin + IPC	70	75 ^{II}	65 ^{II}	TT: 25 ^{II} PL: 75 ^{II}	124	---	---	9
	Warfarin + IPC	69	68 ^{II}	68 ^{II}	TT: 32 ^{II} PL: 68 ^{II}	125	---	---	9
	IPC	73	72 ^{II}	63 ^{III}	TT: 28 ^{II} PL: 72 ^{II}	121	---	---	10
Haas, 1990 Unilateral	Aspirin	36	100	---	---	---	---	RA: 97 [†]	---
	IPC	36	100	---	---	---	---	---	---
Haas, 1990 Bilateral	Aspirin	22	100	---	---	---	---	RA: 97 [†]	---
	IPC	25	100	---	---	---	---	---	---
Sorenson, 1990	Tinzaparin	31	---	---	---	---	---	---	---
	Placebo	33	---	---	---	---	---	---	---
Dechavanne, 1989	Dalteparin 2500U Q12h	41	---	61.9	PL: 88	121.1 (59.1)	---	GA: 100	16.6 (4.8)
	Dalteparin 5000U QD	41	---	46.3	PL: 92	112.4 (34.3)	---	GA: 100	17.1 (4.7)
	Heparin	40	---	56.1	PL: 83	115.1 (51.7)	---	GA: 100	17.2 (5.4)
Monreal, 1989	Dalteparin	46	---	---	---	94 (54)	---	---	---
	Heparin	44	---	---	---	91 (51)	---	---	---
Powers, 1989	Warfarin	65	---	---	---	---	---	---	---
	Aspirin	66	---	---	---	---	---	---	---
	Placebo	63	---	---	---	---	---	---	---
Planes, 1988	Enoxaparin	124	---	62.1	---	63 (30)	138.9 (78.3)	GA: 100	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	Heparin	113	---	69.91	---	66 (23)	141.9 (73.2)	GA: 100	---
Barre, 1987	Dalteparin	40	---	100	---	73.8 (50-115)*	---	RA:100	15.6
	Heparin	40	---	100	---	86.1 (50-160)*	---	RA:100	15.2
Paiement, 1987	Warfarin	72	---	---	---	---	---	---	---
	IPC	66	---	---	---	---	---	---	---
Alfaro, 1986	Aspirin 250mg/d	30	---	---	---	---	---	---	---
	Aspirin 1g/d	30	---	---	---	---	---	---	---
	Control	30	---	---	---	---	---	---	---
Turpie, 1986	Enoxaparin	50	---	---	---	128.84 (26.23)	---	---	---
	Placebo	50	---	---	---	122.78 (23.20)	---	---	---
McKenzie, 1985	General Anesthesia	20	---	---	---	79.4 (4.1)	---	GA: 100	---
	Spinal Anesthesia	20	---	---	---	93.5 (5.6)	---	RA: 100	---
Welin-Berger, 1982	Heparin	20	---	---	---	118	---	---	---
	Control	20	---	---	---	103	---	---	---
Modig, 1981	General Anesthesia	15	---	100	---	161.3 (34.5)	---	GA: 100	---
	Epidural Anesthesia	15	---	100	---	147 (27.9)	---	RA: 100	---
McKenna, 1980	Aspirin	9	---	---	---	---	---	---	16 [‡]
	Placebo	12	---	---	---	---	---	---	

*Mean (range)

†Median (range)

‡Value for the total study population

§Range

||Percent of hips

†Cemented or hybrid prosthesis

Abbreviations: A=anterior; AL=anteriolateral; AM=anteriomedial; ASA=aspirin; BID=twice daily; d=days; DL=direct lateral; GA=general anesthesia; GCS=graduated compression stockings; HFS=hip fracture surgery; IPC=intermittent pneumatic compression device; L=lateral; LOS=length of stay; min=minutes; mg=milligram; ML=midline longitudinal; N=number enrolled; P=posterior; PL=posteriolateral; QD=daily; RA=regional anesthesia; SD=standard deviation; THA=total hip arthroplasty; THR=total hip replacement; TKA= total knee arthroplasty; TKR=total knee replacement; TT=transtrochanteric; UFH=unfractionated heparin; VFP=venous foot pump

Table 8. Baseline characteristics of randomized controlled trials in nonmajor orthopedic surgery

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Varicosity %	Estrogen %	DM %	CA %	CVD %	Previous orthopedic surgery %
Lapidus, 2007	Dalteparin	52	37 (8)	21	80 (12)	17.3	---	0	5.8	0	0	---	---	---
	Placebo	52	42 (9)	21	81 (11)	15.1	---	0	11.3	1.9	3.8	---	---	---
Michot, 2002	Dalteparin	66	42 (14.7)	39.4	---	---	---	---	12.1	6.1	---	0	0	---
	Control	64	46.5 (13.2)	28.1	---	---	---	---	14.1	0	---	0	0	---

Abbreviations: CA=cancer; CVD=cardiovascular disease; DM=diabetes mellitus; Hx=history; kg=kilograms; N=number of participants; SD=standard deviation; Wt=weight

Table 9. Procedural characteristics of randomized controlled trials in nonmajor orthopedic surgery

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Lapidus, 2007	Dalteparin	52	---	---	---	44 (18)	---	GA: 0 RA: 100	---
	Placebo	53	---	---	---	45 (18)	---	GA: 0 RA: 100	---
Michot, 2002	Dalteparin	66	---	---	---	91 (30)	---	GA: 33.3 RA: 66.7 GA+RA: 3.0	---
	Control	64	---	---	---	90 (28)	---	GA: 29.7 RA: 70.3 GA+RA: 3.1	---

Abbreviations: d= days; GA= general anesthesia; LOS= length of stay; N= total number of patients; RA= regional anesthesia; SD= standard deviation

Table 10. Baseline characteristics of observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery.

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Varic- osity %	Estr- ogen %	DM %	CA %	CVD %	Previous ortho- pedic surgery %
Bozic, 2010	Warfarin	51923	67.3 (10.4)	65.17	---	5	12	---	---	---	17	0.6	---	---
	Aspirin	4719	66.4 (10.7)	64.42	---	6	18	---	---	---	16	0.4	---	---
Gerkens, 2010	Enoxaparin	6700	---	---	---	---	---	---	---	---	---	---	---	---
	Fondaparinux	122	---	---	---	---	---	---	---	---	---	---	---	---
	Control	115	---	---	---	---	---	---	---	---	---	---	---	---
Cusick, 2009 THR	Aspirin	2094	68 (19-93)* [†]	---	---	---	---	---	---	---	---	---	---	---
	Warfarin	6		---	---	---	---	---	---	---	---	---	---	---
	Control	86		---	---	---	---	---	---	---	---	---	---	---
Cusick, 2009 TKR	Aspirin	1966	71 (31-93)* [†]	---	---	---	---	---	---	---	---	---	---	---
	Warfarin	5		---	---	---	---	---	---	---	---	---	---	---
	Control	50		---	---	---	---	---	---	---	---	---	---	---
Froimson, 2009	IPC (ActiveCare)	223	66 (11.5)	---	---	---	---	---	---	---	---	---	---	---
	IPC (Flowtron)	1354	64.3 (13.7)	---	---	---	---	---	---	---	---	---	---	---
Gandhi, 2009	Metabolic syndrome	135	66.1 (9.2)	67.00	---	---	---	---	---	---	---	---	---	---
	Without metabolic syndrome	1325	66.6 (9.9)	63.5	---	---	---	---	---	---	---	---	---	---
McNamara, 2009	Thrombosis	117	79(12)	82.91	---	14.02	---	---	---	---	---	---	---	---
	No thrombosis	5183	80 (11)	78.37	---	12.53	---	---	---	---	---	---	---	---
Dorr, 2007	Low risk	856	64.9 (11.9) [†]	56.9 [†]	83.9 (21.1) [†]	---	---	---	---	---	---	---	---	---
	High risk	114		---		---	---	---	---	---	---	---	---	---

Study, Year	Group	N	Age mean (SD)	Female %	Wt kg mean (SD)	Smoker %	Obese %	Hx VTE %	Varic- osity %	Estr- ogen %	DM %	CA %	CVD %	Previous ortho- pedic surgery %
Shorr, 2007	Fondaparinux	12532	69	63.4	---	---	---	---	---	---	---	---	---	---
	Enoxaparin	97827	70	65.2	---	---	---	---	---	---	---	---	---	---
	Dalteparin	16109	68	63.5	---	---	---	---	---	---	---	---	---	---
	UFH	18338	69	63.6	---	---	---	---	---	---	---	---	---	---
	Control	112574	68	63.0	---	---	---	---	---	---	---	---	---	---
Leirozovicz, 2005	sVTE or death	28	72 (68-80)*	67.9	---	---	18.2	3.6	14.3	0.0/ 0.0 [†]	---	7.1	---	---
	No sVTE or death	2392	68 (60-75)*	67.3	---	---	12.1	0.2	4.2	0.2/ 0.5 [‡]	---	3.2	---	---
Sachs, 2003	Warfarin	957	70	56 [†]	---	---	---	---	---	---	---	---	---	---
	Control	785	70		---	---	---	---	---	---	---	---	---	---
Ryan, 1998	Factor V Leiden mutation	32	66.0 (12.1)	47	---	---	---	4	---	---	---	---	---	---
	Without Factor V Leiden mutation	793	66.9 (11.1)	57	---	---	---	8.6	---	---	---	---	---	---
Lieberman, 1997	Before hospital discharge	1042 [†]	59 (19-90)* [†]	---	---	---	---	20 ^{TS}	---	---	---	---	---	---
	After hospital discharge			---	---	---	---		---	---	---	---	---	---
Haas, 1992	No thrombi	498	---	---	---	---	---	---	---	---	---	---	---	---
	Calf thrombi	655	---	---	---	---	---	---	---	---	---	---	---	---
	Proximal thrombi	104	---	---	---	---	---	---	---	---	---	---	---	---
Lemos, 1991	PE	81	---	---	---	---	---	---	---	---	---	---	---	---
	Without PE	159	---	---	---	---	---	---	---	---	---	---	---	---

*Mean(range)

[†]Value for the total study population

[‡]Estrogen/HRT use

§History of symptomatic pulmonary embolism or deep vein thrombosis

Abbreviations: BMI=body mass index; CA=cancer; CVD=cardiovascular disease; DM=diabetes mellitus; hx=history; IPC=intermittent pneumatic compression; kg=kilograms; LMWH=low molecular weight heparin; PE=pulmonary embolism; SD=standard deviation; sVTE=symptomatic venous thromboembolism; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VTE=venous thromboembolism; Wt=weight

Table 11. Procedural characteristics of observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery.

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
Bozic, 2010	Warfarin	51923	100	---	---	---	---	---	3 (3-4)*
	Aspirin	4719	100	---	---	---	---	--	3 (3-4)*
Gerken, 2010	Enoxaparin	6700	---	---	---	---	---	---	---
	Fondaparinux	122	---	---	---	---	---	---	---
	Control	115	---	---	---	---	---	---	---
Cusick, 2009 THR	Aspirin	2094	100	---	P: 100	---	---	---	---
	Warfarin	6	100	---	P: 100	---	---	---	---
	Control	86	100	---	P: 100	---	---	---	---
Cusick, 2009 TKR	Aspirin	1966	100	---	MP: 100	---	---	---	---
	Warfarin	5	100	---	MP: 100	---	---	---	---
	Control	50	100	---	MP: 100	---	---	---	---
Froimson, 2009	IPC (ActiveCare)	223	77.13	---	---	---	---	---	4.2 (3.2)
	IPC (Flowtron)	1354	79.84	---	---	---	---	---	5 (3.7)
Gandhi, 2009	Metabolic syndrome	135	100	---	---	---	---	RA: 100	---
	Without metabolic syndrome	1325	100	---	---	---	---	RA: 100	---
McNamara, 2009	Thrombosis	117	---	---	---	---	60	---	---

Study, Year	Group	N	Primary surgery %	Cemented fixation %	Surgical approach %	Mean duration of surgery min (SD)	Mean duration of anesthesia min (SD)	Anesthesia %	Mean LOS, d
	No thrombosis	5183	---	---	---	---	60	---	---
Dorr, 2007	Low risk	856	100	---	P: 100	---	---	---	---
	High risk	114	100	---	MP: 100	---	---	---	---
Shorr, 2007	Fondaparinux	12532	---	---	---	---	---	---	4.4 (2.6)
	Enoxaparin	97827	---	---	---	---	---	---	5.1 (4.1)
	Dalteparin	16109	---	---	---	---	---	---	4.6 (3.3)
	UFH	18338	---	---	---	---	---	---	5.6 (6.2)
	Control	112574	---	---	---	---	---	---	4.1 (2.5)
Leirozovicz, 2005	sVTE or death	28	100	---	MP: 100	---	---	---	---
	No sVTE or death	2392	100	---	MP: 100	---	---	---	---
Sachs, 2003	Warfarin	957	100	---	---	---	---	---	---
	Control	785	100	---	---	---	---	---	---
Ryan, 1998	Factor V Leiden mutation	32	---	---	---	---	---	---	4.4 (2.6)
	Without Factor V Leiden mutation	793	---	---	---	---	---	---	5.1 (4.1)
Lieberman, 1997	Before hospital discharge	1042 [†]	607 [†]	---	---	---	---	---	11 (4-53) ^{††}
	After hospital discharge								
Haas, 1992	No thrombi	498	100	100	---	---	---	---	---
	Calf thrombi	655	100	100	---	---	---	---	---
	Proximal thrombi	104	100	100	---	---	---	---	---
Lemos, 1991	PE	81	---	---	---	---	---	---	4.6 (3.3)
	Without PE	159	---	---	---	---	---	---	5.6 (6.2)

*Median(range)

†Value for the total population

‡Mean(range)

Abbreviations: d=day(s); GA=general anesthesia; IPC=intermittent pneumatic compression; LMWH=low molecular weight heparin; LOS=length of stay; min=minute; MP=medial parapatellar; N=total population; P=posterior; PE=pulmonary embolism; RA=regional anesthesia; SD=standard deviation; sVTE=symptomatic venous thromboembolism; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin

Appendix F. Additional Evidence Tables

Table 12. Final health outcomes in randomized controlled trials evaluating patients who had major orthopedic surgery

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
Yokote, 2011	Fondaparinux	1/84	---	0/84	0/84	0/84	---	0/84	0/84
	Enoxaparin	0/83	---	0/83	0/83	0/83	---	0/83	0/83
	Placebo	0/83	---	0/83	0/83	0/83	---	0/83	0/83
Fuji, 2010	Dabigatran 150mg	---	2/113	0/126	0/126	0/126	---	0/126	0/126
	Dabigatran 220mg	---	0/102	0/129	0/129	0/129	---	0/129	0/129
	Placebo	---	6/104	0/124	0/124	0/124	---	0/124	0/124
Chin, 2009	Enoxaparin	---	---	---	---	0/110	---	---	---
	Control	---	---	---	---	1/110	---	---	---
Ginsberg, 2009	Dabigatran 150mg QD	---	---	---	---	---	---	1/871	0/871
	Dabigatran 220mg QD	---	---	---	---	---	---	1/857	0/857
	Enoxaparin	---	---	---	---	---	---	0/868	0/868
Edwards, 2008 THA	Enoxaparin + IPC	---	---	0/65	0/65	0/65	---	0/65	0/65
	Enoxaparin	---	---	0/59	0/59	0/59	---	0/59	0/59
Edwards, 2008 TKA	Enoxaparin + IPC	---	---	0/76	1/76	1/76	---	0/76	0/76
	Enoxaparin	---	---	0/77	1/77	1/77	---	0/77	0/77
Fuji, 2008 THA	Enoxaparin 40mg QD	---	---	---	---	1/80	---	---	---
	Enoxaparin 20 mg BID	---	---	---	---	0/90	---	---	---
	Placebo	---	---	---	---	0/86	---	---	---
Fuji, 2008 TKA	Enoxaparin 40mg QD	---	---	---	---	1/74	---	---	---
	Enoxaparin 20 mg BID	---	---	---	---	0/84	---	---	---
	Placebo	---	---	---	---	1/79	---	---	---
Thorey, 2008	Early release tourniquet	---	---	---	---	---	---	---	---
	Late release tourniquet	---	---	---	---	---	---	---	---
Eriksson, 2007a	Dabigatran 150mg QD	---	20/527	0/696	1/696	1/696	---	1/696	0/703
	Dabigatran 220mg QD	---	13/506	0/675	0/675	0/675	---	1/675	0/679
	Enoxaparin	---	18/511	1/685	0/685	1/685	---	1/685	0/694

Study, Year	Group	Symptomatic objectively confirmed VTE n/N		Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
Eriksson, 2007b	Dabigatran 150mg QD	---		38/888	1/1156	0/1156	1/1156	---	3/1156	1/1163
	Dabigatran 220mg QD	---		28/909	0/1137	5/1137	5/1137	---	3/1137	1/1146
	Enoxaparin	---		36/917	0/1142	3/1142	3/1142	---	0/1142	0/1154
Lassen, 2007	Enoxaparin	---		---	0/109	2/109	2/109	---	0/109	0/109
	Warfarin	---		---	0/109	0/109	0/109	---	0/109	0/109
Bonneux, 2006	Fondaparinux	---		---	---	---	---	---	---	---
	Enoxaparin	---		---	---	---	---	---	---	---
Senaran, 2006	Enoxaparin	0/50	2/50*	---	0/50	0/50	0/50	---	0/50	0/50
	Heparin	2/50	0/50*	---	0/50	0/50	0/50	---	0/50	0/50
Westrich, 2006	Minimum hyperflexed knee	---		---	---	---	---	---	---	---
	Standard hyperflexed knee	---		---	---	---	---	---	---	---
Eriksson, 2005	Dabigatran 50mg BID	2/302	2/302 [†]	---	---	0/300 1/302 [†]	---	---	1/389	0/389
	Dabigatran 150mg BID	2/282	1/282 [†]	---	---	2/282 0/282 [†]	---	---	0/390	0/282
	Dabigatran 300mg QD	0/283	2/283 [†]	---	---	0/283 0/283 [†]	---	---	0/385	0/283
	Dabigatran 225mg BID	0/297	0/297 [†]	---	---	0/297 0/297 [†]	---	---	1/393	0/297
	Enoxaparin	1/300	0/300 [†]	---	---	0/300 0/300 [†]	---	---	0/392	0/300
Farag, 2005	Epidural Anesthesia	---		---	---	---	---	---	---	---
	Spinal Anesthesia	---		---	---	---	---	---	---	---
Lachiewicz, 2004	IPC (Venaflo)	---		---	0/206	0/206	0/206	---	0/206	0/206
	IPC (Kendal)	---		---	0/217	1/217	1/217	---	1/217	0/217
Silbersack, 2004	Enoxaparin + IPC	---		---	0/68 [‡]	0/68 [‡]	0/68 [‡]	---	---	---
	Enoxaparin + GCS	---		---	0/63 [‡]	0/63 [‡]	0/63 [‡]	---	---	---
Eriksson, 2003	Extended fondaparinux	1/326		---	0/326	0/326	0/326	---	---	6/327
	Fondaparinux	9/330		---	1/330	2/330	3/330	---	---	8/329
Kim, 2003	Cemented	---		---	---	---	0/200 [§]	---	---	2/200 [§]

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	Non-cemented	---	---	---	---		---	---	
Lassen, 2002	Fondaparinux	12/1129	---	1/1129	3/1129	---	---	2/1140	0/1140
	Enoxaparin	9/1123	---	0/1123	3/1123	---	---	4/1133	0/1133
Pitto, 2002	Bone vacuum cement technique	---	---	0/65	0/65	0/65	---	---	---
	Standard cement technique	---	---	0/65	0/65	0/65	---	---	---
Prandoni, 2002	Extended warfarin	3/184	3/184	0/184	0/184	0/184	---	0/184	0/184
	Warfarin	9/176	9/176	0/176	1/176	1/176	---	0/176	0/176
Turpie, 2002	Fondaparinux	29/1126	---	1/1126	11/1126	---	---	6/1128	0/1126
	Enoxaparin	13/1128	---	2/1128	2/1128	---	---	3/1129	0/1128
Warwick, 2002	Enoxaparin	---	---	0/112	---	---	---	1/112	0/112
	VFP	---	---	2/117	---	---	---	3/117	0/117
Barden, 2001	Modified position	---	---	0/83	0/83	0/83	---	---	---
	Conventional figure four positioning	---	---	0/76	0/76	0/76	---	---	---
Bauer, 2001	Fondaparinux	5/517	---	1/517	2/517	1/517	---	2/517	0/517
	Enoxaparin	10/517	---	1/517	4/517	4/517	---	3/517	0/517
Comp, 2001 THR	Extended enoxaparin	18/224	---	0/224	0/224	0/224	---	0/224	0/224
	Enoxaparin	49/211	---	0/211	1/211	1/211	---	0/211	0/211
Comp, 2001 TKR	Extended enoxaparin	38/217	---	0/217	0/217	0/217	---	0/217	0/217
	Enoxaparin	46/221	---	0/221	2/221	2/221	---	0/221	0/221
Eriksson, 2001	Fondaparinux	17/831	---	8/831	3/831	---	---	38/831	0/831
	Enoxaparin	13/840	---	7/840	4/840	---	---	42/842	1/842
Fitzgerald, 2001	Warfarin	---	---	---	---	1/176	---	3/176	1/176
	Enoxaparin	---	---	---	---	0/173	---	1/173	0/173
Hull, 2000	Dalteparin (pre-operative)	---	---	0/496	0/496	0/496	---	2/496	0/496
	Dalteparin (post-operative)	---	---	0/487	0/487	0/487	---	0/487	0/487
	Warfarin	---	---	0/489	0/489	0/489	---	2/489	0/489
Kennedy, 2000	Aspirin	---	---	---	---	1/73	---	---	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	VFP	---	---	---	---	0/70	---	---	---
Colwell, 1999	Enoxaparin	55/1516	---	1/1516	---	15/1516	---	9/1516	---
	Warfarin	56/1495	---	0/1495	---	12/1495	---	10/1495	---
Levy, 1999	Fibrin adhesive	---	---	0/29	---	---	---	---	---
	No fibrin adhesive	---	---	1/29	---	---	---	---	---
Planes, 1999	Enoxaparin	---	---	1/248	1/248	---	---	1/248	0/248
	Tinzaparin	---	---	0/251	1/251	---	---	0/251	0/251
TIFDED Study Group, 1999	Enoxaparin	---	---	0/66	0/66	0/66	---	---	---
	Dalteparin	---	---	0/66	0/66	0/66	---	---	---
Wakankar, 1999	Tourniquet	---	---	---	---	---	---	1/37	---
	No tourniquet	---	---	---	---	---	---	2/40	---
Kim, 1998	Aspirin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Lassen, 1998	Extended dalteparin	---	---	---	---	---	---	---	---
	Dalteparin	---	---	---	---	---	---	---	---
Rader, 1998	Heparin	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Ryan, 1998	IPC	---	---	0/50	0/50	0/50	---	---	---
	GCS	---	---	0/50	0/50	0/50	---	---	---
Warwick, 1998	Enoxaparin	---	---	0/138	0/138	0/138	---	0/143	0/143
	VFP	---	---	0/136	1/136	1/136	---	0/147	0/147
Andersen, 1997	Extended dalteparin	---	---	---	---	0/20	---	---	---
	Dalteparin	---	---	---	---	1/21	---	---	---
Dahl, 1997	Extended dalteparin	---	---	0/111	0/111	4/111	---	1/134	0/134
	Dalteparin	---	---	1/106	2/106	7/106	---	1/131	0/131
Eriksson, 1997a	Desirudin	---	---	0/180	0/180	0/180	---	0/180	0/180
	UFH	---	---	0/180	4/180	4/180	---	2/180	0/180
Eriksson, 1997b	Desirudin	---	39/802	1/802 ^{II}	---	2/802 1/802 ^{II}	---	4/802	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	Enoxaparin	---	60/785	0/785 ^{II}	---	2/785 5/785 ^{II}	---	1/785	---
Francis, 1997	Dalteparin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
Nilsson, 1997	Extended enoxaparin	2/131	---	0/131	0/131	0/131	---	0/131	0/131
	Enoxaparin	10/131	---	0/131	2/131	2/131	---	0/131	0/131
Planes, 1997	Extended enoxaparin	---	---	0/85	0/85	0/85	---	0/85	0/85
	Enoxaparin	---	---	0/88	0/88	0/88	---	0/88	0/88
Samama, 1997	Enoxaparin	---	---	0/85	0/85	0/85	---	0/85	0/85
	Placebo	---	---	0/84	0/84	0/84	---	0/84	0/84
Eriksson, 1996	Desirudin	---	---	0/202	1/202	1/202	---	0/202	0/202
	UFH	---	---	0/229	0/229	0/229	---	1/229	0/229
Kalodiki, 1996	Enoxaparin + GCS	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Laupacis, 1996	Cemented	---	---	---	---	3/124	---	---	---
	Non-cemented	---	---	---	---	1/125	---	---	---
Leclerc, 1996	Enoxaparin	3/336	---	0/336	1/336	1/336	---	1/336	0/336
	Warfarin	1/334	---	0/334	3/334	3/334	---	1/334	0/334
Lotke, 1996	Aspirin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
Schwartzmann, 1996	Enoxaparin	---	---	0/52	0/52	0/52	---	0/52	0/52
	UFH	---	---	0/47	0/47	0/47	---	0/47	0/47
Stannard, 1996	UFH then aspirin + VFP	---	---	---	---	---	---	0/25	0/25
	UFH then aspirin	---	---	---	---	---	---	0/25	0/25
	VFP	---	---	---	---	---	---	0/25	0/25
Stone, 1996	Enoxaparin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Westrich, 1996	Aspirin + VFP	---	---	---	---	---	---	---	---
	Aspirin	---	---	---	---	---	---	---	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
Williams-Russo, 1996	General Anesthesia	---	---	---	---	3/178 ^{\$}	---	1/81	---
	Regional Anesthesia	---	---	---	---		---	1/97	---
Abdel-Salam, 1995	Tourniquet	---	---	---	---	---	---	---	---
	No tourniquet	---	---	---	---	---	---	---	---
Avikainen, 1995	Enoxaparin	---	---	---	---	0/83	---	---	---
	UFH	---	---	---	---	1/84	---	---	---
Colwell, 1995	Enoxaparin	---	---	0/228	0/228	0/228	---	---	---
	Heparin	---	---	1/225	1/225	2/225	---	---	---
Warwick, 1995	Enoxaparin	---	---	---	---	1/78	---	---	---
	Control	---	---	---	---	2/78	---	---	---
Colwell, 1994	Enoxaparin 30mg Q12h	---	---	0/195	0/195 0/195*	0/195	0/195*	---	1/195
	Enoxaparin 40mg QD	---	---	0/203	0/203 0/203*	0/203	0/203*	---	0/203
	UFH	---	---	0/209	1/209 3/209*	1/209	3/209*	---	2/209
Fauno, 1994	Enoxaparin	---	---	0/92	0/92	0/92	---	---	---
	UFH	---	---	0/93	0/93	0/93	---	---	---
Leiberman, 1994	Aspirin + IPC	---	---	0/113	0/113	1/113	---	1/113	0/113
	Aspirin	---	---	0/118	0/118	1/118	---	0/118	0/118
Menzin, 1994	UFH	---	---	---	---	---	---	---	---
	Enoxaparin 40mg QD	---	---	---	---	---	---	---	---
	Enoxaparin 30mg Q12h	---	---	---	---	---	---	---	---
Santori, 1994	Heparin	---	---	---	---	---	---	1/65	0/65
	VFP	---	---	---	---	---	---	0/67	0/67
Hull, 1993 THR	Tinzaparin	6/398 [¶]	---	0/398 [¶]	1/398 [¶]	1/398 [¶]	---	5/715 [#]	0/398
	Warfarin	2/397 [¶]	---	0/397 [¶]	0/397 [¶]	0/397 [¶]	---	5/721 [#]	0/397
Hull, 1993 TKR	Tinzaparin	1/317 [¶]	---	0/317 [¶]	0/317 [¶]	0/317 [¶]			0/317
	Warfarin	1/324	---	0/324 [¶]	1/324 [¶]	1/324 [¶]			0/324
Fordyce, 1992	VFP	---	---	---	---	---	---	---	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	Control	---	---	---	---	---	---	---	---
Francis, 1992	Warfarin	---	---	---	---	---	---	1/103	0/103
	IPC	---	---	---	---	---	---	1/98	0/98
Jorgensen, 1992	Dalteparin	---	---	---	---	---	---	3/30	0/30
	Placebo	---	---	---	---	---	---	4/38	0/38
Wilson, 1992	VFP	---	---	0/28	0/28	0/28	---	---	---
	Control	---	---	0/32	0/32	0/32	---	---	---
Bailey, 1991	Warfarin	---	---	---	---	---	---	0/45	0/45
	IPC	---	---	---	---	---	---	0/50	0/50
Eriksson, 1991	Dalteparin	---	---	0/65	8/65	8/65	---	0/67	0/67
	UFH	---	---	0/62	19/62	19/62	---	1/69	0/69
Jorgensen, 1991	General Anesthesia	---	---	---	1/22	---	---	---	---
	Epidural Anesthesia	---	---	---	0/17	---	---	---	---
Lassen, 1991	Tinzaparin	---	---	0/93	1/93	1/93	---	1/93	---
	Placebo	---	---	0/97	1/97	1/97	---	1/97	---
Levine, 1991	Enoxaparin	---	---	0/333	0/333	0/333	---	0/333	0/333
	UFH	---	---	0/332	2/332	2/332	---	0/332	0/332
Mitchell, 1991	General Anesthesia	---	---	---	---	---	---	---	---
	Epidural Anesthesia	---	---	---	---	---	---	---	---
Planes, 1991	General Anesthesia + Enoxaparin	---	---	0/62	0/62	0/62	---	0/62	0/62
	Epidural Anesthesia + Enoxaparin	---	---	0/61	0/61	0/61	---	1/61	0/61
	Epidural Anesthesia alone	---	---	0/65	0/65	0/65	---	0/65	0/65
Torholm, 1991	Dalteparin	---	---	---	---	---	---	1/58	0/58
	Placebo	---	---	---	---	---	---	0/54	0/54
Woolson, 1991	Aspirin + IPC	---	---	---	---	1/70	---	---	---
	Warfarin + IPC	---	---	---	---	0/69	---	---	---
	IPC	---	---	---	---	0/73	---	---	---
Haas, 1990 Unilateral TKA	Aspirin	---	---	---	---	---	---	---	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	IPC	---	---	---	---	---	---	---	---
Haas, 1990 Bilateral TKA	Aspirin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Sorensen, 1990	Tinzaparin	---	---	---	---	---	---	1/31	0/31
	Placebo	---	---	---	---	---	---	1/33	0/33
Dechavanne, 1989	Dalteparin 2500U Q12h	---	---	---	---	---	---	---	---
	Dalteparin 5000U QD	---	---	---	---	---	---	---	---
	Heparin	---	---	---	---	---	---	---	---
Monreal, 1989	Dalteparin	---	---	0/46	6/46	6/46	---	2/46	0/46
	Heparin	---	---	0/44	0/44	0/44	---	3/44	1/44
Powers, 1989	Warfarin	---	---	0/65	0/65	0/65	---	5/65	0/65
	Aspirin	---	---	1/66	0/66	1/66	---	5/66	0/66
	Placebo	---	---	0/63	2/63	2/63	---	3/63	0/63
Planes, 1988	Enoxaparin	---	---	0/120	0/120	---	---	0/120	0/120
	Heparin	---	---	0/108	1/108	---	---	0/108	0/108
Barre, 1987	Dalteparin	---	---	0/40	0/40	0/40	---	0/40	0/40
	Heparin	---	---	0/40	0/40	0/40	---	0/40	0/40
Palement, 1987	Warfarin	---	---	0/72	0/72	0/72	---	---	---
	IPC	---	---	0/66	0/66	0/66	---	---	---
Alfaro, 1986	Aspirin 250mg/d	---	---	---	---	0/30	---	---	---
	Aspirin 1g/d	---	---	---	---	0/30	---	---	---
	Control	---	---	---	---	1/30	---	---	---
Turpie, 1986	Enoxaparin	---	---	0/50	0/50	0/50	---	0/50	0/50
	Placebo	---	---	0/50	1/50	1/50	---	1/50	1/50
McKenzie, 1985	General Anesthesia	---	---	---	---	---	---	5/20	---
	Spinal Anesthesia	---	---	---	---	---	---	3/20	---
Welin-Berger, 1982	Heparin	---	---	---	---	0/20	---	---	---
	Control	---	---	---	---	1/20	---	---	---
Modig, 1981	General Anesthesia	---	---	---	---	7/15	---	---	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	Epidural Anesthesia	---	---	---	---	2/15	---	---	---
McKenna, 1980	Aspirin	---	---	---	---	---	---	0/9	0/9
	Placebo	---	---	---	---	---	---	0/12	0/12

*Discharge-42days; †After study period-30 or 42days; ‡42-82days;§number of events out of the total population; ||After study period-42days; ¶Discharge-90days; #number of events out of combined THR and TKR population

Abbreviations: BID=twice daily; d=days; g=grams; GCS=graduated compression stockings; h=hours; IPC=intermittent pneumatic compression device; mg=milligram; n/N= total number of events/total population; PE=pulmonary embolism; PTS=post thrombotic syndrome; QD=daily; SD=standard deviation; THA=total hip arthroplasty; THR=total hip replacement; TKA=total knee arthroplasty; TKR=total knee replacement; U=units; UFH=unfractionated heparin; VFP=venous foot pump; VTE=venous thromboembolism

Table 13. Final health outcomes in randomized controlled trials evaluating nonmajor orthopedic surgery

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Non- fatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
Lapidus, 2007	Dalteparin	---	---	0/52	0/52	0/52	---	---	---
	Placebo	---	---	0/53	0/53	0/53	---	---	---
Michot, 2002	Dalteparin	---	---	---	---	1/66	---	---	---
	Control	---	---	---	---	0/64	---	---	---

Abbreviations: n/N= total number of events/total population; PE=pulmonary embolism; PTS=post thrombotic syndrome; VTE=venous thromboembolism

Table 14. Final health outcomes in observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
Bozic, 2010	Warfarin	---	---	---	---	---	---	54/51923	---
	Aspirin	---	---	---	---	---	---	9/4719	---
Gerken, 2010	Enoxaparin	---	---	---	---	---	---	149/6700	18/6700
	Fondaparinux	---	---	---	---	---	---	1/122	0/122
	Control	---	---	---	---	---	---	13/115	1/115
Cusick, 2009 THR	Aspirin	---	---	1/2094	27/4060*	---	---	5/2094	---
	Warfarin	---	---	0/6	0/11*	---	---	0/6	---

Study, Year	Group	Symptomatic objectively confirmed VTE n/N	Major VTE n/N	Fatal PE n/N	Nonfatal PE n/N	PE n/N	PTS n/N	Mortality n/N	Mortality due to bleeding n/N
	Control	---	---	0/86	0/136*	---	---	0/86	---
Cusick, 2009 TKR	Aspirin	---	---	2/1966		---	---	8/1966	---
	Warfarin	---	---	0/5		---	---	0/5	---
	Control	---	---	0/50		---	---	0/50	---
Froimson, 2009	IPC (ActiveCare)	---	---	0/223	0/223	---	---	0/223	0/223
	IPC (Flowtron)	---	---	0/1354	9/1354	---	---	0/1354	0/1354
Shorr, 2007	Fondaparinux	---	---	---	---	---	---	75/12532	---
	Enoxaparin or dalteparin	---	---	---	---	---	---	1253/113936	---
	UFH	---	---	---	---	---	---	403/18338	---
	Control	---	---	---	---	---	---	---	---
Sachs, 2003	Warfarin	---	---	---	---	---	---	1/957	---
	Control	---	---	---	---	---	---	2/785	---

* The nonfatal PE data reflect the entire study population. THR and TKR was not broken down.

Abbreviations: IPC=intermittent pneumatic compression; PE=pulmonary embolism; PTS=post-thrombotic syndrome; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VTE=venous thromboembolism

Table 15. Intermediate health outcomes from randomized controlled trials evaluating patients who had major orthopedic surgery

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Yokote, 2011	Fondaparinux	6/84	---	1/84	1/84	6/84
	Enoxaparin	5/83	---	0/83	0/83	5/83
	Placebo	6/83	---	0/83	0/83	6/83
Fuji, 2010	Dabigatran 150mg	34/104	32/104	2/126	2/113	---
	Dabigatran 220mg	23/96	22/96	1/129	0/102	---
	Placebo	57/101	55/101	2/124	6/104	---
Chin, 2009	Enoxaparin	6/110	---	---	1/110	5/110
	Control	24/110	---	---	3/110	21/110
Ginsberg, 2009	Dabigatran 150mg QD	---	---	6/649	20/649	198/649
	Dabigatran 220mg QD	---	---	7/604	14/604	167/604
	Enoxaparin	---	---	5/643	10/643	148/643

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Edwards, 2008 THA	Enoxaparin + IPC	1/65	---	---	0/65	1/65
	Enoxaparin	2/59	---	---	0/59	2/59
Edwards, 2008 TKA	Enoxaparin + IPC	5/76	---	---	0/76	5/76
	Enoxaparin	8/77	---	---	0/77	8/77
Fuji, 2008 THA	Enoxaparin 40mg QD	27/80	---	---	6/80	---
	Enoxaparin 20 mg BID	18/90	---	---	3/90	---
	Placebo	36/86	---	---	9/86	---
Fuji, 2008 TKA	Enoxaparin 40mg QD	25/74	---	---	3/74	---
	Enoxaparin 20 mg BID	25/84	---	---	0/84	---
	Placebo	48/79	---	---	6/79	---
Thorey, 2008	Early release tourniquet	0/20	0/20	0/20	0/20	0/20
	Late release tourniquet	0/20	0/20	0/20	0/20	0/20
Eriksson, 2007a	Dabigatran 150mg QD	---	208/524	3/696	---	---
	Dabigatran 220mg QD	---	181/503	1/675	---	---
	Enoxaparin	---	184/511	8/685	---	---
Eriksson, 2007b	Dabigatran 150mg QD	---	63/871	9/1156	---	---
	Dabigatran 220mg QD	---	40/874	6/1137	---	---
	Enoxaparin	---	56/894	1/1142	---	---
Lassen, 2007	Enoxaparin	---	14/109	1/109	1/109	---
	Warfarin	---	28/109	1/109	2/109	---
Bonneux, 2006	Fondaparinux	---	---	2/55	---	---
	Enoxaparin	---	---	1/54	---	---
Senaran, 2006	Enoxaparin	0/50	---	2/50*	---	---
	Heparin	2/50	---	0/50*	---	---
Westrich, 2006	Minimum hyperflexed knee	30/79 [†]	---	---	13/79 [†]	---
	Standard hyperflexed knee	39/93 [†]	---	---	11/92 [†]	---
Eriksson, 2005 THR	Dabigatran 50mg BID	49/208	---	2/302 [‡]	1/302 ^{‡§}	12/208
	Dabigatran 150mg BID	26/201	---	0/282 [‡]	1/282 ^{‡§}	8/201
	Dabigatran 300mg QD	25/191	---	0/283 [‡]	2/283 ^{‡§}	3/191
	Dabigatran 225mg BID	17/204	---	0/297 [‡]	0/297 ^{‡§}	4/204
	Enoxaparin	31/208	---	1/300 [‡]	0/300 ^{‡§}	11/208

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Eriksson, 2005 TKR	Dabigatran 50mg BID	37/94	---	2/302 [†]	1/302 ^{†§}	3/94
	Dabigatran 150mg BID	21/81	---	0/282 [†]	1/282 ^{†§}	1/81
	Dabigatran 300mg QD	22/92	---	0/283 [†]	2/283 ^{†§}	3/92
	Dabigatran 225mg BID	22/93	---	0/297 [†]	0/297 ^{†§}	1/93
	Enoxaparin	41/92	---	1/300 [†]	0/300 ^{†§}	6/92
Frag, 2005	Epidural Anesthesia	0/10	0/10	0/10	0/10	0/10
	Spinal Anesthesia	0/14	0/14	0/14	0/14	0/14
Lachiewicz, 2004	IPC (Venaflow)	16/232	---	0/206	1/232	15/232
	IPC (Kendal)	36/240	---	0/217	6/240	30/240
Silbersack, 2004	Enoxaparin + IPC	0/68	---	---	0/68	0/68
	Enoxaparin + GCS	18/63	---	---	2/63	16/63
Eriksson, 2003	Extended fondaparinux	3/208	---	1/326	2/221	1/207
	Fondaparinux	74/218	---	6/330	35/222	42/211
Kim, 2003	Cemented	31/150	---	---	19/150	22/150
	Non-cemented	41/150	---	---	23/150	30/150
Lassen, 2002	Fondaparinux	36/908	---	3/1129	6/922	30/909
	Enoxaparin	83/918	---	1/1123	23/927	67/917
Pitto, 2002	Bone vacuum cement technique	2/65	---	---	0/65	2/65
	Standard cement technique	12/65	---	---	7/65	5/65
Prandoni, 2002	Extended warfarin	3/184	1/184	2/184	1/184	---
	Warfarin	8/176	5/176	3/176	3/176	---
Turpie, 2002	Fondaparinux	44/784	---	5/1126	14/816	34/796
	Enoxaparin	65/796	---	0/1128	10/830	54/800
Warwick, 2002	Enoxaparin	48/89	---	---	0/89	48/89
	VFP	57/99	---	---	4/99	53/99
Barden, 2001	Modified position	---	---	0/83	---	---
	Conventional figure four positioning	---	---	3/76	---	---
Bauer, 2001	Fondaparinux	45/361	---	3/517	9/368	35/372
	Enoxaparin	98/361	---	4/517	20/372	78/366
Comp, 2001 THR	Extended enoxaparin	18/224	---	---	6/224	12/224

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Comp, 2001 TKR	Enoxaparin	49/211	---	---	27/211	22/211
	Extended enoxaparin	38/217	---	---	9/217	29/217
	Enoxaparin	46/221	---	---	17/221	27/221
Eriksson, 2001	Fondaparinux	49/624	---	1/831	6/650	42/627
	Enoxaparin	117/623	---	1/840	28/646	94/626
Fitzgerald, 2001	Warfarin	79/176	---	---	20/176	75/176
	Enoxaparin	44/173	---	---	3/173	44/173
Hull, 2000	Dalteparin (pre-operative)	36/337	---	5/337	3/354	---
	Dalteparin (post-operative)	44/336	---	10/336	3/358	---
	Warfarin	81/338	---	15/338	11/363	---
Kennedy, 2000	Aspirin	7/73	3/73	4/73	---	---
	VFP	4/70	2/70	2/70	4/70	---
Colwell, 1999	Enoxaparin	---	---	49/1516	---	---
	Warfarin	---	---	47/1495	---	---
Levy, 1999	Fibrin adhesive	0/29	0/29	0/29	0/29	0/29
	No fibrin adhesive	0/29	0/29	0/29	0/29	0/29
Planes, 1999	Enoxaparin	44/219	---	3/219	23/219	21/219
	Tinzaparin	48/221	---	2/221	21/221	27/221
TIFDED Study Group, 1999	Enoxaparin	8/52	8/52	0/52	2/52	---
	Dalteparin	5/57	5/57	0/57	3/57	---
Wakankar, 1999	Tourniquet	1/37	1/37	---	1/37	0/37
	No tourniquet	0/40	0/40	---	0/40	0/40
Kim, 1998	Aspirin	6/50	---	---	---	---
	Control	10/50	---	---	---	---
Lassen, 1998	Extended dalteparin	5/113	3/113	---	1/111	---
	Dalteparin	12/102	9/102	---	5/101	---
Rader, 1998 THA	Heparin	1/56	---	---	---	---
	Enoxaparin	2/70	---	---	---	---
Rader, 1998 TKA	Heparin	1/60	---	---	---	---
	Enoxaparin	6/60	---	---	---	---

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Ryan, 1998	IPC	---	---	0/50	4/50	---
	GCS	---	---	0/50	11/50	---
Warwick, 1998	Enoxaparin	18/138	---	1/138	12/138	6/138
	VFP	24/136	---	0/136	17/136	7/136
Andersen, 1997	Extended dalteparin	2/20	1/20	1/20	---	---
	Dalteparin	3/21	2/21	1/21	---	---
Dahl, 1997	Extended dalteparin	11/93 [¶]	---	8/114	10/114	---
	Dalteparin	2/89 [¶]	---	4/104	14/104	---
Eriksson, 1997a	Desirudin	13/180	---	2/180 [#]	5/174	---
	UFH	42/180	---	3/180 [#]	28/177	---
Eriksson, 1997b	Desirudin	142/773	---	6/773 [#]	36/802	---
	Enoxaparin	196/768	---	3/768 [#]	59/785	---
Francis, 1997	Dalteparin	28/192	---	---	10/192	21/192
	Warfarin	49/190	---	---	16/190	43/190
Nilsson, 1997	Extended enoxaparin	21/131	19/131	2/131	8/131	13/131
	Enoxaparin	43/131	35/131	8/131	28/131	15/131
Planes, 1997	Extended enoxaparin	6/85	---	---	5/85	1/85
	Enoxaparin	17/88	---	---	7/88	10/88
Samama, 1997	Enoxaparin	11/78	10/78	1/78	2/78	8/78
	Placebo	28/75	27/75	1/75	12/75	13/75
Eriksson, 1996	Desirudin	37/202	---	---	6/195	---
	UFH	77/229	---	---	43/219	---
Kalodiki, 1996	Enoxaparin + GCS	8/32	---	---	4/32	---
	Enoxaparin	12/32	---	---	9/32	---
	Placebo	13/14	---	---	8/14	---
Laupacis, 1996	Cemented	36/72	---	---	2/67	36/72
	Non-cemented	33/70	---	---	3/63	32/69
Leclerc, 1996	Enoxaparin	76/336	---	---	24/336	---
	Warfarin	109/334	---	---	22/334	---
Lotke, 1996	Aspirin	94/166	---	---	16/166	---
	Warfarin	78/146	---	---	18/146	---
Schwartzmann, 1996	Enoxaparin	5/52	2/52	3/52	4/52	1/52

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
	UFH	5/47	2/47	3/47	5/47	0/47
Stannard, 1996	UFH then aspirin + VFP	0/25	0/25	0/25	0/25	0/25
	UFH then aspirin	5/25	2/25	3/25	5/25	0/25
	VFP	0/25	0/25	0/25	0/25	0/25
Stone, 1996	Enoxaparin	1/25	1/25	0/25	1/25	0/25
	IPC	1/25	1/25	0/25	1/25	0/25
Westrich, 1996	Aspirin + VFP	11/41	22/81 [†]	---	0/41	0/81 [†]
	Aspirin	26/39	49/83 [†]	---	5/39	12/83 [†]
Williams-Russo, 1996	General Anesthesia	39/81	---	---	0/81	39/81
	Regional Anesthesia	39/97	---	---	0/97	39/97
Abdel-Salam, 1995	Tourniquet	4/40	---	---	4/40	0/40
	No tourniquet	0/40	---	---	0/40	0/40
Avikainen, 1995	Enoxaparin	1/83	---	1/83	1/83	0/83
	UFH	4/84	---	4/84	4/84	0/84
Colwell, 1995	Enoxaparin	56/228	---	---	5/228	51/228
	Heparin	77/225	---	---	22/225	54/225
Warwick, 1995	Enoxaparin	22/78	---	---	12/78	10/78
	Control	33/78	---	---	14/78	19/78
Colwell, 1994	Enoxaparin 30mg Q12h	9/194	---	---	4/194	4/194
	Enoxaparin 40mg QD	30/203	---	---	8/203	20/203
	UFH	24/207	---	---	10/207	11/207
Fauno, 1994	Enoxaparin	21/92	---	0/92**	3/92	18/92
	UFH	25/93	---	1/93**	5/93	20/93
Leiberman, 1994	Aspirin + IPC	---	---	---	0/124 ^{††}	1/126 ^{††}
	Aspirin	---	---	---	7/124 ^{††}	8/126 ^{††}
Menzin, 1994	UFH	24/209	---	---	---	---
	Enoxaparin 40mg QD	30/202	---	---	---	---
	Enoxaparin 30mg Q12h	9/192	---	---	---	---
Santori, 1994	Heparin	23/65	---	---	---	---
	VFP	9/67	---	---	---	---
Hull, 1993 THR	Tinzaparin	69/332	---	---	16/332	---
	Warfarin	79/340	---	---	13/340	---

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Hull, 1993 TKR	Tinzaparin	116/258	---	---	20/258	---
	Warfarin	152/277	---	---	34/277	---
Fordyce, 1992	VFP	4/39	---	---	2/39	2/39
	Control	16/40	---	---	5/40	3/40
Francis, 1992	Warfarin	32/103	---	---	3/103	---
	IPC	26/98	---	---	12/98	---
Jorgensen, 1992	Dalteparin	5/30	---	---	---	---
	Placebo	18/38	---	---	---	---
Wilson, 1992	VFP	14/28 [†]	---	---	0/28 [†]	5/28 [†]
	Control	22/32 [†]	---	---	6/32 [†]	13/32 [†]
Bailey, 1991	Warfarin	12/45	---	---	0/45	---
	IPC	3/50	---	---	2/50	---
Eriksson, 1991	Dalteparin	19/63	17/63	2/63	---	---
	UFH	25/59	23/59	2/59	---	---
Lassen, 1991	Tinzaparin	29/93	29/93	0/93	24/93	5/93
	Placebo	44/97	44/97	0/97	35/97	9/97
Jorgensen, 1991	General Anesthesia	13/22	11/22	2/22	3/22	10/22
	Epidural Anesthesia	3/17	3/17	0/17	1/17	2/17
Levine, 1991	Enoxaparin	50/258	---	---	14/258	---
	UFH	61/263	---	---	17/263	---
Mitchell, 1991	General Anesthesia				24/38	
	Epidural Anesthesia				16/34	
Planes, 1991	General Anesthesia + Enoxaparin	---	---	---	4/62	0/62
	Epidural Anesthesia + Enoxaparin	---	---	---	4/60	3/60
	Epidural Anesthesia alone	---	---	---	4/65	7/65
Torholm, 1991	Dalteparin	8/58	---	---	0/58	8/58
	Placebo	16/54	---	---	4/54	12/54
Woolson, 1991	Aspirin + IPC	---	---	---	7/72 ^{††}	---
	Warfarin + IPC	---	---	---	6/69 ^{††}	---
	IPC	---	---	---	9/76 ^{††}	---

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Haas, 1990 Unilateral TKA	Aspirin	17/36	---	---	0/36	17/36
	IPC	8/36	---	---	0/36	8/36
Haas, 1990 Bilateral TKA	Aspirin	15/22	---	---	1/22	14/22
	IPC	12/25	---	---	2/25	10/25
Sorensen, 1990	Tinzaparin	17/31	---	---	---	---
	Placebo	16/33	---	---	---	---
Dechavanne, 1989	Dalteparin 2500U Q12h	2/41	---	---	1/41	1/41
	Dalteparin 5000U QD	3/41	---	---	1/41	2/41
	Heparin	4/40	---	---	3/40	1/40
Monreal, 1989	Dalteparin	14/32	---	---	12/32	2/32
	Heparin	6/30	---	---	5/30	1/30
Powers, 1989	Warfarin	---	---	---	---	---
	Aspirin	---	---	---	---	---
	Placebo	---	---	---	---	---
Planes, 1988	Enoxaparin	15/120	---	---	9/120	6/120
	Heparin	27/108	---	---	20/108	7/108
Barre, 1987	Dalteparin	7/40	---	---	---	---
	Heparin	4/40	---	---	---	---
Paiement, 1987	Warfarin	12/72	---	---	5/72	8/72
	IPC	11/66	---	---	10/66	2/66
Alfaro, 1986	Aspirin 250mg/d	1/30	---	---	---	---
	Aspirin 1g/d	1/30	---	---	---	---
	Control	9/30	---	---	---	---
Turpie, 1986	Enoxaparin	4/37	---	---	2/37	---
	Placebo	20/39	---	---	9/39	---
McKenzie, 1985	General Anesthesia	15/20	15/20	0/20	---	---
	Spinal Anesthesia	8/20	5/20	3/20	---	---
Welin-Berger, 1982	Heparin	8/20	---	---	---	---
	Control	5/20	---	---	---	---
Modig, 1981	General Anesthesia	11/15	---	---	11/15	11/15
	Epidural Anesthesia	5/15	---	---	3/15	4/15

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
McKenna, 1980	Aspirin	7/9	---	---	3/9	4/9
	Placebo	9/12	---	---	5/12	4/12

*Discharge-42days

†Number of events out of total knees

‡Number of events out of the combined THR and TKR population

§After study period-30 or 42days

||Discharge to 180days

¶7-35days; After study period-42days

**Discharge-60days

††Number of events out of total hips

Abbreviations: BID=twice daily; d=day; DVT=deep vein thrombosis; g=gram; GCS=graduated compression stockings; h=hours; IPC=intermittent pneumatic compression device; mg=milligram; n/N= total number of events/total population; QD=daily; THA=total hip arthroplasty; THR=total hip replacement; TKA=total knee arthroplasty; TKR=total knee replacement; U=units; UFH=unfractionated heparin; VFP=venous foot pump

Table 16. Intermediate health outcomes in randomized controlled trials evaluating patients who had nonmajor orthopedic surgery

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Lapidus, 2007	Dalteparin	18/49	---	---	1/49	---
	Placebo	19/47	---	---	3/47	---
Michot, 2002	Dalteparin	1/66	---	---	0/66	1/66
	Control	10/64	---	---	0/64	10/64

Abbreviations: N=number of participants; n=number of participants with the event

Table 17. Intermediate health outcomes in observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery

Study, Year	Group	DVT n/N	Asymptomatic DVT n/N	Symptomatic DVT n/N	Proximal DVT n/N	Distal DVT n/N
Bozic, 2010	Warfarin	---	---	---	---	---
	Aspirin	---	---	---	---	---
Gerkens, 2010	Enoxaparin	---	---	---	---	---
	Fondaparinux	---	---	---	---	---
	Control	---	---	---	---	---
Cusick, 2009 THR	Aspirin	---	---	---	---	---
	Warfarin	---	---	---	---	---
	Control	---	---	---	---	---
Cusick, 2009 TKR	Aspirin	---	---	---	---	---
	Warfarin	---	---	---	---	---
	Control	---	---	---	---	---
Froimson, 2009	IPC (ActiveCare)	3/223	---	---	---	---
	IPC (Flowtron)	49/1354	---	---	---	---
Shorr, 2007	Fondaparinux	---	---	---	---	---
	Enoxaparin or dalteparin	---	---	---	---	---
	UFH	---	---	---	---	---
	Control	---	---	---	---	---
Sachs, 2003	Warfarin	---	---	2/957	---	---
	Control	---	---	0/785	---	---

Abbreviations: DVT=deep vein thrombosis; IPC=intermittent pneumatic compression; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin

Table 18. Major and minor bleeding from randomized controlled trials evaluating patients who had major orthopedic surgery

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Yokote, 2011	Fondaparinux	0/85	Retroperitoneal, intracranial, intraocular, if it was associated with either death, transfusion of more than 2 Units of packed RBCs or whole blood, a reduction in the level of Hb >2g/dL or a serious life threatening clinical event requiring medical intervention	7/85	One of the following: epistaxis lasting >5min or requiring intervention, ecchymosis or hematoma with maximum size of >5 cm hematuria not associated with trauma from urinary catheter, GI hemorrhage not related to intubation or passage of a nasogastric tube, wound hematoma, or hemorrhagic wound complication, not associated with major hemorrhage or subconjunctival hemorrhage requiring cessation of medications
	Enoxaparin	0/85		6/85	
	Placebo	0/85		2/85	
Fuji, 2010	Dabigatran 150mg	0/126	Fatal bleeding; clinically overt bleeding associated with a fall \geq Hb 20g/L, transfusion of \geq 2U PRBC or whole blood, retroperitoneal or intracranial bleeding, bleeding warranting treatment cessation	12/126	Per European guidelines
	Dabigatran 220mg	3/129		9/129	
	Placebo	1/124		6/124	
Chin, 2009	Enoxaparin	---	---	---	---
	Control	---	---	---	---
Ginsberg, 2009	Dabigatran 150mg	5/871 2/871*	Fatal bleeding; clinically overt bleeding in excess of expected and associated with a fall of 2g/L of Hb and/or leading to transfusion of \geq 2U packed cells or whole blood; symptomatic retroperitoneal, intracranial, intraocular, or intraspinal bleeding; bleeding requiring treatment cessation and/or operation	22/871 5/871*	Spontaneous skin hematoma >25 cm ² ; wound hematoma >100 cm ² ; spontaneous nose bleeding or gingival bleeding lasting >5 min; spontaneous rectal bleeding creating more than a spot on toilet paper; macroscopic hematuria either spontaneous or, if associated with an intervention (e.g. Foley catheter) lasting >24h; other bleeding event considered clinically relevant by the investigator not qualifying as a major bleed
	Dabigatran 220mg	5/857 1/857*		23/857 6/857*	
	Enoxaparin	12/868 0/868*		21/868 3/868*	
Edwards, 2008 THA	Enoxaparin + IPC	---	---	---	---
	Enoxaparin	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Edwards, 2008 TKA	Enoxaparin + IPC	---	---	---	---
	Enoxaparin	---	---	---	---
Fuji, 2008 THA	Enoxaparin 40mg QD	2/102	Retroperitoneal, intracranial, or intraocular; associated with death, transfusion of ≥ 2 U of PRBC or whole blood (not autologous), reduction in Hb ≥ 2 g/dl; serious or life-threatening clinical event that required medical intervention	7/102	Epistaxis lasting >5 min or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; hematuria not associated with urinary catheter trauma; GI hemorrhage not related to intubation or NG tube; wound hematoma or hemorrhagic wound complications not associated with major hemorrhage; subconjunctival hemorrhage requiring cessation of medication
	Enoxaparin 20mg BID	3/104		4/104	
	Placebo	0/101		2/101	
Fuji, 2008 TKA	Enoxaparin 40mg QD	1/91	Retroperitoneal, intracranial, or intraocular; associated with death, transfusion of ≥ 2 U of PRBC or whole blood (not autologous), reduction in Hb ≥ 2 g/dl; serious or life-threatening clinical event that required medical intervention	6/91	Epistaxis lasting >5 min or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; hematuria not associated with urinary catheter trauma; GI hemorrhage not related to intubation or NG tube; wound hematoma or hemorrhagic wound complications not associated with major hemorrhage; subconjunctival hemorrhage requiring cessation of medication
	Enoxaparin 20mg BID	3/95		10/95	
	Placebo	4/89		4/89	
Thorey, 2008	Early release tourniquet	---	---	---	---
	Late release tourniquet	---	---	---	---
Eriksson, 2007a	Dabigatran 150mg QD	9/703	Defined according to accepted guidelines	59/703	Defined according to accepted guidelines
	Dabigatran 220mg QD	10/679		60/679	
	Enoxaparin	9/694		69/694	
Eriksson, 2007b	Dabigatran 150mg QD	15/1163	Defined according to accepted guidelines	72/1163	Defined according to accepted guidelines
	Dabigatran 220mg QD	23/1146		70/1146	
	Enoxaparin	18/1154		74/1154	

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Lassen, 2007	Enoxaparin	0/149	Accompanied by a reduction in Hb of >2 g/dl (relative to the postsurgical value) and/or a requirement for transfusion of > 2U of blood product; need to discontinue study medication; intracranial, intraspinal, retroperitoneal, or in the operated joint necessitating re-operation or intervention, intrapericardial, intraocular or fatal	6/149	Defined as other bleeding not meeting the definition of "major"
	Warfarin	0/151		8/151	
Bonneux, 2006	Fondaparinux	---	---	---	---
	Enoxaparin	---	---	---	---
Senaran, 2006	Enoxaparin	2/50	Overt bleeding associated with ≥1 of the following events: death or a life-threatening clinical event; bleeding confirmed to be retroperitoneal, intracranial, intraocular; postoperative transfusion of >2U of PRBC or whole blood; decrease in the Hb > 20g/L compared with the relevant postoperative level	1/50	Overt bleeding episode that did not meet the criterion for classification as a major bleeding episode, or absence of any simultaneous bleeding other than the surgical wound
	Heparin	0/50		4/50	
Westrich, 2006	Minimum hyperflexed knee	---	---	---	---
	Standard hyperflexed knee	---	---	---	---
Eriksson, 2005 THR	Dabigatran 50mg BID	0/265	Clinically overt bleeding associated with > 20 g/L fall in Hb; clinically overt leading to transfusion of >2U packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation	11/265	Minor bleeding events were defined as those not fulfilling the criteria of major or clinically significant bleeding
	Dabigatran 150mg BID	10/266		23/266	
	Dabigatran 300mg QD	12/258		22/258	

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Eriksson, 2005 TKR	Dabigatran 225mg BID	12/270	Clinically overt bleeding associated with >20 g/L fall in Hb; clinically overt leading to transfusion of >2U packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation	28/270	Minor bleeding events were defined as those not fulfilling the criteria of major or clinically significant bleeding
	Enoxaparin	6/270		14/270	
	Dabigatran 50mg BID	1/124		7/124	
	Dabigatran 150mg BID	6/124		8/124	
	Dabigatran 300mg QD	6/127		15/127	
	Dabigatran 225mg BID	3/123		10/123	
	Enoxaparin	2/122		11/122	
Frag, 2005	Epidural Anesthesia	---	---	---	---
	Spinal Anesthesia	---	---	---	---
Lachiewicz, 2004	IPC (Venaflow)	---	---	---	---
	IPC (Kendal)	---	---	---	---
Silbersack, 2004	Enoxaparin + IPC	---	---	---	---
	Enoxaparin + GCS	---	---	---	---
Eriksson, 2003	Extended fondaparinux	8/327	Fatal, retroperitoneal, intracranial, or intraspinal bleeding; bleeding that involved any other critical organ; bleeding leading to reoperation; overt bleeding with a bleeding index ≥ 2	5/327	---
	Fondaparinux	2/329		2/329	---
Kim, 2003	Cemented	---	---	---	---
	Non-cemented	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Lassen, 2002	Fondaparinux	47/1140	Fatal, retroperitoneal, intracranial, or intraspinal bleeding; bleeding that involved any other critical organ; bleeding leading to reoperation; overt bleeding with a bleeding index ≥ 2	---	---
	Enoxaparin	32/1133		---	---
Pitto, 2002	Bone vacuum cement technique	0/65	Major bleeding from a wound (wound hematoma requiring operative decompression), or major bleeding not related to a wound (gastrointestinal or intracerebral hemorrhage).	5/65	Minor bleeding from a wound (bleeding at the injection site, epistaxis, or wound hematoma not requiring operative decompression)
	Standard cement technique	0/65		4/65	
Prandoni, 2002	Extended warfarin	1/184	Clinically overt bleeding associated with either a decrease in Hb ≥ 2 g/dL or a need for a transfusion of ≥ 2 U RBC; intracranial or retroperitoneal; resulted in the permanent discontinuation of anticoagulation	---	---
	Warfarin	0/176		---	---
Turpie, 2002	Fondaparinux	20/1128	Fatal, retroperitoneal, intracranial, or intraspinal bleeding; bleeding that involved any other critical organ; bleeding leading to reoperation; overt bleeding with a bleeding index ≥ 2	---	---
	Enoxaparin	11/1129		---	---
Warwick, 2002	Enoxaparin	---	---	---	---
	VFP	---	---	---	---
Barden, 2001	Modified position	---	---	---	---
	Conventional figure four positioning	---	---	---	---
Bauer, 2001	Fondaparinux	11/517	Fatal, retroperitoneal, intracranial, or intraspinal bleeding; bleeding that involved any other critical organ; bleeding leading to reoperation; overt bleeding with a bleeding index ≥ 2	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
	Enoxaparin	1/517		---	---
Comp, 2001 THR	Extended enoxaparin	0/224	Clinically overt bleeding resulting in death, transfusion of ≥ 2 U blood products, decrease in the Hb level of ≥ 2.0 g/dL (≥ 20 g/L) compared with the most recent preceding postoperative value; serious or life-threatening clinical event; one requiring surgical intervention; retroperitoneal, intracranial, or intraocular in location	---	Overt bleeding that did not meet the criteria for major hemorrhage and associated with ≥ 1 of the following: epistaxis lasting more than 5min or requiring intervention, ecchymosis or hematoma >5 cm at its greatest dimension, hematuria not associated with urinary catheter related trauma, GI hemorrhage not related to intubation or placement of a NG tube, wound hematoma or complications, subconjunctival hemorrhage necessitating cessation of medication
	Enoxaparin	0/211		---	
Comp, 2001 TKR	Extended enoxaparin	0/217	Clinically overt bleeding resulting in death, transfusion of ≥ 2 U blood products, decrease in the Hb level of ≥ 2.0 g/dL (≥ 20 g/L) compared with the most recent preceding postoperative value; serious or life-threatening clinical event; one requiring surgical intervention; retroperitoneal, intracranial, or intraocular in location	---	Overt bleeding that did not meet the criteria for major hemorrhage and associated with ≥ 1 of the following: epistaxis lasting more than 5min or requiring intervention, ecchymosis or hematoma >5 cm at its greatest dimension, hematuria not associated with urinary catheter related trauma, GI hemorrhage not related to intubation or placement of a NG tube, wound hematoma or complications, subconjunctival hemorrhage necessitating cessation of medication
	Enoxaparin	1/221		---	
Eriksson, 2001	Fondaparinux	18/831	Fatal, retroperitoneal, intracranial, or intraspinal bleeding; bleeding that involved any other critical organ; bleeding leading to reoperation; overt bleeding with a bleeding index ≥ 2	34/831	Overt bleeding that did not meet the criteria for major bleeding
	Enoxaparin	19/842		18/842	
Fitzgerald, 2001	Warfarin	4/176	Fulfilled ≥ 1 of the following: resulted in transfusion of ≥ 2 U PRBC; resulted in a decrease in the Hb ≥ 20 g/L compared with the postoperative Hb concentration before the administration of any study medication; retroperitoneal, intracranial, or intraocular; resulted in a serious life-threatening clinical event or death	37/176	---
	Enoxaparin	9/173		49/173	

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Hull, 2000	Dalteparin (pre-operative)	33/496 [†] 11/496 [‡]	Clinically overt and associated with a decrease in Hb≥20 g/L or required transfusion of ≥ 2U of blood; intracranial, intraocular, intraspinal or retroperitoneal; occurred into a prosthetic joint	3/496 [†] 6/496 [‡]	Clinically overt without meeting the major bleeding criteria and as trivial if it was clearly of no consequence
	Dalteparin (post-operative)	28/487 [†] 4/487 [‡]		3/487 [†] 8/487 [‡]	
	Warfarin	20/489 [†] 2/489 [‡]		2/489 [†] 8/489 [‡]	
Kennedy, 2000	Aspirin	---	---	---	---
	VFP	---	---	---	---
Colwell, 1999	Enoxaparin	18/1516	Overt bleeding associated with ≥1 of the following: death or life threatening clinical event; bleeding confirmed to be retroperitoneal, intracranial, or intraocular; post-operative blood transfusion ≥2U PRBC or whole blood; decrease in Hb>20g/L	143/1516	Overt bleeding that did not meet the criteria for major bleeding
	Warfarin	8/1495		106/1495	
Levy, 1999	Fibrin adhesive	---	---	---	---
	No fibrin adhesive	---	---	---	---
Planes, 1999	Enoxaparin	4/248	Overt and associated with either a fall in Hb≥2g/dl, need for transfusion of ≥2U blood, or if retroperitoneal, intracranial, or intraocular	21/248	Overt bleeding not meeting the criteria for major bleeding
	Tinzaparin	2/251		13/251	
TIFDED Study Group, 1999	Enoxaparin	2/66	Bleeding leading to death or re-operation; intracranial bleeding; bleeding into organs; associated with a decrease in Hb>32g/L within 72h	---	Other bleedings (e.g. small wound hematoma or oozing)
	Dalteparin	1/66		---	
Wakankar, 1999	Tourniquet	---	---	---	---
	No tourniquet	---	---	---	---
Kim, 1998	Aspirin	0/50	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
	Control	0/50	---	---	---
Lassen, 1998	Extended dalteparin	0/140	---	18/140	---
	Dalteparin	1/141	---	11/141	---
Rader, 1998	Heparin	---	---	---	---
	Enoxaparin	---	---	---	---
Ryan, 1998	IPC (Kendal)	---	---	---	---
	GCS	---	---	---	---
Warwick, 1998	Enoxaparin	---	---	---	---
	VFP	---	---	---	---
Andersen, 1997	Extended dalteparin	---	---	---	---
	Dalteparin	---	---	---	---
Dahl, 1997	Extended dalteparin	---	---	---	---
	Dalteparin	---	---	---	---
Eriksson, 1997a	Desirudin	---	---	---	---
	UFH	---	---	---	---
Eriksson, 1997b	Desirudin	20/1028	Serious bleeding defined as any of the following: perioperative transfusion of $\geq 5U$ of whole blood, red-cell concentrate, or both; transfusion of $\geq 7U$ whole blood, red-cell concentrate, or both, at any time; transfusion of a total of >3500 mL of blood	---	---
	Enoxaparin	20/1023		---	---
Francis, 1997	Dalteparin	6/271	Bleeding which was fatal or if they required a transfusion, reoperation, or prolonged hospital stay	16/271	Minor bleeding in the GI or urinary tract and hematoma at the site of an injection
	Warfarin	4/279		10/279	
Nilsson, 1997	Extended enoxaparin	---	---	---	---
	Enoxaparin	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Planes, 1997	Extended enoxaparin	0/90	Overt bleeding associated with a decrease in Hb ≥ 2 g/dL compared with the last postoperative value; need for transfusion of ≥ 2 U PRBC; retroperitoneal or intracranial	17/90	Overt bleeding that did not meet the criteria for major hemorrhage
	Enoxaparin	0/89		4/89	
Samama, 1997	Enoxaparin	1/78	Overt, associated with decrease in Hb ≥ 2 /dl or required ≥ 2 transfusions; Intracranial, retroperitoneal, or led to surgical intervention or death	32/78	Overt but did not meet criteria for "major"
	Placebo	1/75		21/75	
Eriksson, 1996	Desirudin	---	---	---	---
	UFH	---	---	---	---
Kalodiki, 1996	Enoxaparin + GCS	---	---	---	---
	Enoxaparin	---	---	---	---
	Placebo	---	---	---	---
Laupacis, 1996	Cemented	---	---	---	---
	Non-cemented	---	---	---	---
Leclerc, 1996	Enoxaparin	7/336	Overt bleeding that decreased the Hb ≥ 20 g/L, necessitated transfusion of ≥ 2 U packed red cells, hemarthrosis requiring evacuation, discontinuation of prophylaxis, or interruption of physiotherapy for at least 24 hours	94/336	Overt bleeding not meeting the criteria for major hemorrhage
	Warfarin	6/334		83/334	
Lotke, 1996	Aspirin	---	---	---	---
	Warfarin	---	---	---	---
Schwartzmann, 1996	Enoxaparin	---	---	---	---
	UFH	---	---	---	---
Stannard, 1996	UFH then aspirin + VFP	---	---	---	---
	UFH then aspirin	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
	VFP	---	---	---	---
Stone, 1996	Enoxaparin	---	---	---	---
	IPC	---	---	---	---
Westrich, 1996	Aspirin + VFP	0/61	---	0/61	---
	Aspirin	0/61	---	0/61	---
Williams-Russo, 1996	General Anesthesia	---	---	---	---
	Regional Anesthesia	---	---	---	---
Abdel-Salam, 1995	Tourniquet	---	---	---	---
	No tourniquet	---	---	---	---
Avikainen, 1995	Enoxaparin	---	---	---	---
	UFH	---	---	---	---
Colwell, 1995	Enoxaparin	3/228	---	43/228	---
	Heparin	3/225	---	49/225	---
Warwick, 1995	Enoxaparin	---	---	---	---
	Control	---	---	---	---
Colwell, 1994	Enoxaparin 30mg Q12h	8/195	Overt bleeding associated with ≥1 of the following: death or a life threatening clinical event; acute MI or stroke; bleeding at the operative site; retroperitoneal, intracranial or GI; postoperative transfusion >2U PRBC; decrease in Hb >20g/L compared with the relevant post-operative value	16/195	Overt bleeding episode that did not meet the criteria for classification of a major episode
	Enoxaparin 40mg QD	3/203		18/203	
	UFH	13/209		12/209	
Fauno, 1994	Enoxaparin	---	---	---	---
	UFH	---	---	---	---
Leiberman, 1994	Aspirin + IPC	---	---	---	---
	Aspirin	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Menzin, 1994	UFH	13/209	Overt and associated with death or life threatening clinical event, a decrease in Hb from baseline of >20g/L or a post-operative transfusion >2U of non-autologous blood	---	---
	Enoxaparin 40mg QD	3/202		---	---
	Enoxaparin 30mg Q12h	8/192		---	---
Santori, 1994	Heparin	---	---	---	---
	VFP	---	---	---	---
Hull, 1993 THR	Tinzaparin	11/398	---	5/398	---
	Warfarin	6/397	---	9/397	---
Hull, 1993 TKR	Tinzaparin	9/317	---	5/317	---
	Warfarin	3/324	---	5/324	---
Fordyce, 1992	VFP	---	---	---	---
	Control	---	---	---	---
Francis, 1992	Warfarin	---	---	3/103	Hematemesis , hemoptysis, hematuria
	IPC	---	---	4/98	
Jorgensen, 1992	Dalteparin	---	---	---	---
	Placebo	---	---	---	---
Wilson, 1992	VFP	---	---	---	---
	Control	---	---	---	---
Bailey, 1991	Warfarin	---	---	---	---
	IPC	---	---	---	---
Eriksson, 1991	Dalteparin	0/67	---	---	---
	UFH	0/69	---	---	---
Jorgensen, 1991	General Anesthesia	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
	Epidural Anesthesia	---	---	---	---
Lassen, 1991	Tinzaparin	---	---	---	---
	Placebo	---	---	---	---
Levine, 1991	Enoxaparin	11/333	Overt and associated with either a fall in Hb level $\geq 2\text{g/L}$, a need for transfusion of $\geq 2\text{U}$ of blood, or retroperitoneal or intracranial	6/333	Overt bleeding not meeting criteria for major bleeding
	UFH	19/332		12/332	
Mitchell, 1991	General Anesthesia	---	---	---	---
	Epidural Anesthesia	---	---	---	---
Planes, 1991	General Anesthesia + Enoxaparin	2/62	NR	0/62	NR
	Epidural Anesthesia + Enoxaparin	1/61		0/61	
	Epidural Anesthesia alone	1/65		0/65	
Torholm, 1991	Dalteparin	---	---	---	---
	Placebo	---	---	---	---
Woolson, 1991	Aspirin + IPC	---	---	---	---
	Warfarin + IPC	---	---	---	---
	IPC	---	---	---	---
Haas, 1990 Unilateral TKA	Aspirin	---	---	---	---
	IPC	---	---	---	---
Haas, 1990 Bilateral TKA	Aspirin	---	---	---	---
	IPC	---	---	---	---
Sorensen, 1990	Tinzaparin	---	---	---	---
	Placebo	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Dechavanne, 1989	Dalteparin 2500U Q12h	---	---	---	---
	Dalteparin 5000U QD	---	---	---	---
	Heparin	---	---	---	---
Monreal, 1989	Dalteparin	---	---	---	---
	Heparin	---	---	---	---
Powers, 1989	Warfarin	5/65	Overt and associated with a decrease in Hb $\geq 20\text{g/l}$; led to transfusion of $\geq 2\text{U}$ of blood; retroperitoneal or intracranial bleeding	---	---
	Aspirin	1/66		---	---
	Placebo	5/63		---	---
Planes, 1988	Enoxaparin	2/124	Overt and associated with either a fall in Hb level $\geq 2\text{g/dl}$, need for transfusion of $\geq 2\text{U}$ of blood, or if it was retroperitoneal or intracranial	1/124	Overt but did not meet the other criteria for major bleeding
	Heparin	0/112		2/112	
Barre, 1987	Dalteparin	---	---	---	---
	Heparin	---	---	---	---
Paiement, 1987	Warfarin	0/72	Overt and associated with a decrease in the Hb $\geq 2\text{ g/dL}$; led to transfusion of $\geq 2\text{U}$ of blood; retroperitoneal, intracranial or occurred in a major prosthetic joint	3/72	Minor post-operative wound bleed
	IPC	0/66		3/66	
Alfaro, 1986	Aspirin 250mg/d	---	---	---	---
	Aspirin 1g/d	---	---	---	---
	Control	---	---	---	---
Turpie, 1986	Enoxaparin	1/50	Overt, associated with decrease in Hb $\geq 2\text{dL}$; required transfusion of $\geq 2\text{U}$ of blood; intracranial or retroperitoneal	1/50	Overt bleeding that did not meet criteria for "major"
	Placebo	2/50		0/50	
McKenzie, 1985	General Anesthesia	---	---	---	---
	Spinal Anesthesia	---	---	---	---

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Welin-Berger, 1982	Heparin	---	---	---	---
	Control	---	---	---	---
Modig, 1981	General Anesthesia	---	---	---	---
	Epidural Anesthesia	---	---	---	---
McKenna, 1980	Aspirin	---	---	---	---
	Placebo	---	---	---	---

*After study period-90days

†Days 0-1

‡Days 2-8

Abbreviations: BID=twice daily; cm=centimeters; d=day; dL=deciliter; DVT=deep vein thrombosis; g=gram; GCS=graduated compression stockings; GI=gastrointestinal; h=hours; Hb=hemoglobin; HFS=hip fracture surgery; IPC=intermittent pneumatic compression; mg=milligram; min=minutes; mL=milliliter; N=number of participants; n=number of participants with the event; NG=nasogastric; PRBC=packed red blood cells; QD= once daily; RBC=red blood cell; THA=total hip arthroplasty; THR=total hip replacement; TKA=total knee arthroplasty; TKR=total knee replacement; U=units; UFH=unfractionated heparin; VFP=venous foot pump

Table 19. Bleeding outcomes in randomized controlled trials evaluating patients who had nonmajor orthopedic surgery

Study, Year	Group	Major Bleeding n/N	Major Bleeding Definition	Minor Bleeding n/N	Minor Bleeding Definition
Lapidus, 2007	Dalteparin	0/52	Bleeding requiring blood transfusion or bleeding in a critical site (such as intraocular, intracranial, intraspinal, or retroperitoneal bleeding)	---	---
	Placebo	0/53		---	---
Michot, 2002	Dalteparin	0/66	Overt bleeding associated with transfusion of packed red blood cells or surgical interventions or when it led to permanent disability.	8/66	Overt bleeding that did not meet the other criteria for major hemorrhage (soft-tissue hematoma at the operation site or at the LMWH injection site, hemarthrosis, GI bleeding).
	Control	0/64		4/64	

Abbreviations: N=number of participants; n=number of participants with the event

Table 20. Major and minor bleeding outcomes in observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery

Study, Year	Group	Major bleeding n/N	Major bleeding definition	Minor bleeding n/N	Minor bleeding definition
Bozic, 2010	Warfarin	---	---	---	---
	Aspirin	---	---	---	---
Gerken, 2010	Enoxaparin	71/6700	Major bleeding was defined as bleeding in a critical organ, that is retroperitoneal bleeding, cerebral bleeding, ocular bleeding, gastrointestinal bleeding, or urinary bleeding	---	---
	Fondaparinux	0/122		---	---
	Control	1/115		---	---
Cusick, 2009 THR	Aspirin	---	---	---	---
	Warfarin	---	---	---	---
	Control	---	---	---	---
Cusick, 2009 TKR	Aspirin	---	---	---	---
	Warfarin	---	---	---	---
	Control	---	---	---	---
Froimson, 2009	IPC (ActiveCare)	---	---	---	---
	IPC (Flowtron)	---	---	---	---
Shorr, 2007	Fondaparinux	188/12532	ICD-9 codes for hemoperitoneum bleed (568.81), intracranial hemorrhage/hemorrhagic stroke (430-432), hemorrhage complicating a procedure (98.11), or other bleeding accompanied by greater than 2 units of blood transfused as recorded in the billing file	---	---
	Enoxaparin or dalteparin	1709/113936		---	---
	UFH	---		---	---
	Control	---		---	---
Sachs, 2003	Warfarin	---	---	---	---
	Control	---	---	---	---

Abbreviations: ICD-9=International Classification of Disease, Ninth Revision; IPC=intermittent pneumatic compression; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin

Table 21. Adverse outcomes from randomized controlled trials evaluating patients who had major orthopedic surgery

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
Yokote, 2011	Fondaparinux	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Fuji, 2010	Dabigatran 150mg	0/126	---	---	0/126	---	---	---	---
	Dabigatran 220mg	1/129	---	---	1/129	---	---	---	---
	Placebo	0/124	---	---	0/124	---	---	---	---
Chin, 2009	Enoxaparin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Ginsberg, 2009	Dabigatran 150mg QD	0/871	3/871	---	---	---	---	---	---
	Dabigatran 220mg QD	0/857	2/857	---	---	---	---	---	---
	Enoxaparin	1/868	11/868	---	---	---	---	---	---
Edwards, 2008 THA	Enoxaparin + IPC	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Edwards, 2008 TKA	Enoxaparin + IPC	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Fuji, 2008 THA	Enoxaparin 40mg QD	---	---	---	---	---	---	---	---
	Enoxaparin 20mg BID	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Fuji, 2008 TKA	Enoxaparin 40mg QD	---	---	---	---	---	---	---	---
	Enoxaparin 20mg BID	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Thorey, 2008	Early release tourniquet	---	---	---	---	---	---	---	---
	Late release tourniquet	---	---	---	---	---	---	---	---
Eriksson, 2007a	Dabigatran 150mg QD	1/703	---	---	6/703	---	---	---	---
	Dabigatran 220mg QD	3/679	---	---	8/679	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Enoxaparin	1/694	---	---	5/694	---	---	---	---
Eriksson, 2007b	Dabigatran 150mg QD	3/1163	---	---	8/1163	---	---	---	---
	Dabigatran 220mg QD	2/1146	---	---	21/1146	---	---	---	---
	Enoxaparin	3/1154	---	---	16/1154	---	---	---	---
Lassen, 2007	Enoxaparin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
Bonneux, 2006	Fondaparinux	---	---	---	---	---	---	---	4/55
	Enoxaparin	---	---	---	---	---	---	---	1/54
Senaran, 2006	Enoxaparin	---	3/50	---	---	0/50	---	2/50	---
	Heparin	---	4/50	---	---	0/50	---	0/50	---
Westrich, 2006	Minimum hyperflexed knee	---	---	---	---	---	---	---	---
	Standard hyperflexed knee	---	---	---	---	---	---	---	---
Eriksson, 2005	Dabigatran 50mg BID	---	---	---	---	---	---	---	---
	Dabigatran 150mg BID	---	---	---	---	---	---	---	---
	Dabigatran 300mg QD	---	---	---	---	---	---	---	---
	Dabigatran 225mg BID	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Frag, 2005	Epidural Anesthesia	---	---	---	---	---	---	---	---
	Spinal Anesthesia	---	---	---	---	---	---	---	---
Lachiewicz, 2004	IPC (Venaflow)	---	---	---	---	---	---	---	---
	IPC (Kendal)	---	---	---	---	---	---	---	---
Silbersack, 2004	Enoxaparin + IPC	---	---	---	---	---	---	---	---
	Enoxaparin + GCS	---	---	---	---	---	---	---	---
Eriksson, 2003	Extended fondaparinux	2/327	6/327	0/327	29/327	---	---	---	---
	Fondaparinux	2/329	0/329	0/329	20/329	---	---	---	---
Kim, 2003	Cemented	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Non-cemented	---	---	---	---	---	---	---	---
Lassen, 2002	Fondaparinux	5/1140	40/1140	---	---	---	---	---	---
	Enoxaparin	3/1133	29/1133	---	---	---	---	---	---
Pitto, 2002	Bone vacuum cement technique	---	---	---	---	---	---	---	---
	Standard cement technique	---	---	---	---	---	---	---	---
Prandoni, 2002	Extended warfarin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
Turpie, 2002	Fondaparinux	2/1128	---	---	---	---	---	---	---
	Enoxaparin	2/1129	---	---	---	---	---	---	---
Warwick, 2002	Enoxaparin	---	---	---	---	---	---	3/112	---
	VFP	---	---	---	---	---	---	4/117	---
Barden, 2001	Modified position	---	---	---	---	---	---	---	---
	Conventional figure four positioning	---	---	---	---	---	---	---	---
Bauer, 2001	Fondaparinux	2/517	---	---	---	---	---	---	---
	Enoxaparin	1/517	---	---	---	---	---	---	---
Comp, 2001 THR	Extended enoxaparin	---	---	---	---	---	---	3/224	---
	Enoxaparin	---	---	---	---	---	---	22/211	---
Comp, 2001 TKR	Extended enoxaparin	---	---	---	---	---	---	7/217	---
	Enoxaparin	---	---	---	---	---	---	12/221	---
Eriksson, 2001	Fondaparinux	3/831	---	---	---	---	---	---	---
	Enoxaparin	2/842	---	---	---	---	---	---	---
Fitzgerald, 2001	Warfarin	0/176	6/176	---	---	---	---	---	0/176
	Enoxaparin	0/173	12/173	---	---	---	---	---	0/173

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
Hull, 2000	Dalteparin (pre-operative)	---	32/496 [*] 9/496 [†] 0/496 [‡] 0/496 [§]	---	---	---	---	---	---
	Dalteparin (post-operative)	---	27/487 [*] 3/487 [†] 1/487 [‡] 2/487 [§]	---	---	---	---	---	---
	Warfarin	---	17/489 [*] 2/489 [†] 0/489 [‡] 0/489 [§]	---	---	---	---	---	---
Kennedy, 2000	Aspirin	---	---	---	---	---	---	---	---
	VFP	---	---	---	---	---	---	---	---
Colwell, 1999	Enoxaparin	---	62/1516 14/1516 [¶]	---	---	0/1516	---	---	---
	Warfarin	---	45/1495 5/1495 [¶]	---	---	0/1495	---	---	---
Levy, 1999	Fibrin adhesive	---	---	---	---	---	---	---	---
	No fibrin adhesive	---	---	---	---	---	---	---	---
Planes, 1999	Enoxaparin	---	4/248	---	---	1/248	---	---	---
	Tinzaparin	---	2/251	---	---	0/251	---	---	---
TIFDED Study Group, 1999	Enoxaparin	---	0/66	---	---	---	---	---	---
	Dalteparin	---	1/66	---	---	---	---	---	---
Wakankar, 1999	Tourniquet	---	---	---	---	---	---	---	---
	No tourniquet	---	---	---	---	---	---	---	---
Kim, 1998	Aspirin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Lassen, 1998	Extended dalteparin	---	---	---	---	---	---	---	---
	Dalteparin	---	---	---	---	---	---	---	---
Rader, 1998	Heparin	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Enoxaparin	---	---	---	---	---	---	---	---
Ryan, 1998	IPC (Kendal)	---	---	---	---	---	---	---	---
	GCS	---	---	---	---	---	---	---	---
Warwick, 1998	Enoxaparin	---	---	---	---	---	17/122	1/143	---
	VFP	---	---	---	---	---	35/124	1/147	---
Andersen, 1997	Extended dalteparin	---	---	---	---	---	---	---	0/20
	Dalteparin	---	---	---	---	---	---	---	2/21
Dahl, 1997	Extended dalteparin	---	---	---	---	---	---	---	---
	Dalteparin	---	---	---	---	---	---	---	---
Eriksson, 1997a	Desirudin	0/225				---			
	UFH	0/220				---			
Eriksson, 1997b	Desirudin	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Francis, 1997	Dalteparin	1/271	12/271	---	5/271	---	---	---	41/192
	Warfarin	0/279	3/279	---	3/279	---	---	---	48/190
Nilsson, 1997	Extended enoxaparin	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
Planes, 1997	Extended enoxaparin	---	---	---	0/90	---	---	---	---
	Enoxaparin	---	---	---	0/89	---	---	---	---
Samama, 1997	Enoxaparin	0/78	---	---	---	---	---	---	---
	Placebo	0/75	---	---	---	---	---	---	---
Eriksson, 1996	Desirudin	4/277	8/277	---	---	---	---	---	---
	UFH	2/277	7/277	---	---	---	---	---	---
Kalodiki, 1996	Enoxaparin + GCS	---	---	---	---	---	---	---	---
	Enoxaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Laupacis, 1996	Cemented	---	---	---	---	---	---	---	---
	Non-cemented	---	---	---	---	---	---	---	---
Leclerc, 1996	Enoxaparin	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Warfarin	---	---	---	---	---	---	---	---
Lotke, 1996	Aspirin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
Schwartzmann, 1996	Enoxaparin	---	---	---	---	---	---	---	---
	UFH	---	---	---	---	---	---	---	---
Stannard, 1996	UFH then aspirin + VFP	---	---	---	---	---	---	---	---
	UFH then aspirin	---	---	---	---	---	---	---	---
	VFP	---	---	---	---	---	---	---	---
Stone, 1996	Enoxaparin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Westrich, 1996	Aspirin+ VFP	---	---	---	---	---	---	---	---
	Aspirin	---	---	---	---	---	---	---	---
Williams-Russo, 1996	General Anesthesia	---	---	---	---	---	---	---	---
	Regional Anesthesia	---	---	---	---	---	---	---	---
Abdel-Salam, 1995	Tourniquet	---	---	---	---	---	---	---	---
	No tourniquet	---	---	---	---	---	---	---	---
Avikainen, 1995	Enoxaparin	---	---	---	---	---	---	---	---
	UFH	---	---	---	---	---	---	---	---
Colwell, 1995	Enoxaparin	---	9/228	---	---	---	---	---	---
	Heparin	---	5/225	---	---	---	---	---	---
Warwick, 1995	Enoxaparin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Colwell, 1994	Enoxaparin 30mg Q12h	---	6/195	---	---	0/195	---	3/195	---
	Enoxaparin 40mg QD	---	1/203	---	---	0/203	---	1/203	---
	UFH	---	7/209	---	---	1/209	---	4/209	---
Fauno, 1994	Enoxaparin	---	---	---	---	---	---	---	---
	UFH	---	---	---	---	---	---	---	---
Lieberman, 1994	Aspirin + IPC	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Aspirin	---	---	---	---	---	---	---	---
Menzin, 1994	UFH	---	---	---	---	---	---	---	---
	Enoxaparin 40mg QD	---	---	---	---	---	---	---	---
	Enoxaparin 30mg Q12h	---	---	---	---	---	---	---	---
		---	---	---	---	---	---	---	---
Santori, 1994	Heparin	---	---	---	---	---	---	---	---
	VFP	---	---	---	---	---	---	---	---
Hull, 1993	Tinzaparin	---	18/715	---	---	---	---	---	---
			0/715 [¶]						
	Warfarin	---	7/721	---	---	---	---	---	---
			1/721 [¶]						
Fordyce, 1992	VFP	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Francis, 1992	Warfarin	0/103	---	---	0/103	---	---	---	---
	IPC	0/98	---	---	0/98	---	---	---	---
Jorgensen, 1992	Dalteparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Wilson, 1992	VFP	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Bailey, 1991	Warfarin	---	---	---	---	---	---	0/45	---
	IPC	---	---	---	---	---	---	1/50	---
Eriksson, 1991	Dalteparin	0/67	---	---	---	---	---	---	---
	UFH	0/69	---	---	---	---	---	---	---
Jorgensen, 1991	General Anesthesia	---	---	---	---	---	---	---	---
	Epidural Anesthesia	---	---	---	---	---	---	---	---
Lassen, 1991	Tinzaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Levine, 1991	Enoxaparin	---	---	---	---	0/333	---	---	---
	UFH	---	---	---	---	9/332	---	---	---
Mitchell, 1991	General Anesthesia	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Epidural Anesthesia	---	---	---	---	---	---	---	---
Planes, 1991	General Anesthesia + Enoxaparin	---	---	---	---	---	---	---	---
	Epidural Anesthesia + Enoxaparin	---	---	---	---	---	---	---	---
	Epidural Anesthesia alone	---	---	---	---	---	---	---	---
Torholm, 1991	Dalteparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Woolson, 1991	Aspirin + IPC	---	---	---	---	---	---	---	---
	Warfarin + IPC	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Haas, 1990 Unilateral TKA	Aspirin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Haas, 1990 Bilateral TKA	Aspirin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Sorensen, 1990	Tinzaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Dechavanne, 1989	Dalteparin 2500U Q12h	---	---	---	---	---	---	---	---
	Dalteparin 5000U QD	---	---	---	---	---	---	---	---
	Heparin	---	---	---	---	---	---	---	---
Monreal, 1989	Dalteparin	---	---	---	---	---	---	---	---
	Heparin	---	---	---	---	---	---	---	---
Powers, 1989	Warfarin	---	---	---	---	---	---	---	---
	Aspirin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Planes, 1988	Enoxaparin	---	---	---	---	---	---	---	---
	Heparin	---	---	---	---	---	---	---	---
Barre, 1987	Dalteparin	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Heparin	---	---	---	---	---	---	---	---
Paiement, 1987	Warfarin	---	---	---	---	---	---	---	---
	IPC	---	---	---	---	---	---	---	---
Alfaro, 1986	Aspirin 250mg/d	---	---	---	---	---	---	---	---
	Aspirin 1g/d	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Turpie, 1986	Enoxaparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
McKenzie, 1985	General Anesthesia	---	---	---	---	---	---	---	---
	Spinal Anesthesia	---	---	---	---	---	---	---	---
Welin-Berger, 1982	Heparin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Modig, 1981	General Anesthesia	---	---	---	---	---	---	---	---
	Epidural Anesthesia	---	---	---	---	---	---	---	---
McKenna, 1980	Aspirin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---

* major surgical bleeding on days 0-1

†major surgical bleeding on days 2-8

‡minor surgical bleeding on days 0-1

§minor surgical bleeding on days 2-8

||minor surgical site bleeding

¶major surgical site bleeding

Abbreviations: BID=twice daily; d=day; g=gram; GCS= graduated compression stockings; h=hours; HFS=hip fracture surgery; HIT=heparin-induced thrombocytopenia; IPC=intermittent pneumatic compression device; mg=milligram; n/N= total number of events/total population; QD=daily; THA=total hip arthroplasty; THR=total hip replacement; TKA=total knee arthroplasty; TKR=total knee replacement; U=units; UFH=unfractionated heparin; VFP=venous foot pump

Table 22. Adverse outcomes in randomized controlled trials evaluating nonmajor orthopedic surgery

Study, Year	Group	Major bleeding leading to re-operation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Re-admission n/N	Re-operation n/N
Lapidus, 2007	Dalteparin	---	---	---	---	---	---	---	---
	Placebo	---	---	---	---	---	---	---	---
Michot, 2002	Dalteparin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---

Abbreviations: HIT= heparin induced thrombocytopenia; N=number of participants; n=number of participants with the event

Table 23. Additional adverse events in observational studies evaluating venous thromboembolism prophylaxis in major orthopedic surgery

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
Bozic, 2010	Warfarin	---	548/51923	---	---	---	---	---	---
	Aspirin	---	30/4719	---	---	---	---	---	---
Gerken, 2010	Enoxaparin	---	---	---	---	---	---	---	---
	Fondaparinux	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Cusick, 2009 THR	Aspirin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Cusick, 2009 TKR	Aspirin	---	---	---	---	---	---	---	---
	Warfarin	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Froimson, 2009	IPC (ActiveCare)	---	---	---	---	---	---	---	---
	IPC (Flowtron)	---	---	---	---	---	---	---	---
Shorr, 2007	Fondaparinux	---	---	---	---	---	---	---	---

Study, Year	Group	Major bleeding leading to reoperation n/N	Surgical site bleeding n/N	Bleeding leading to infection n/N	Bleeding leading to transfusion n/N	HIT n/N	Discomfort n/N	Readmission n/N	Reoperation n/N
	Enoxaparin or dalteparin	---	---	---	---	---	---	---	---
	UFH	---	---	---	---	---	---	---	---
	Control	---	---	---	---	---	---	---	---
Sachs, 2003	Warfarin	---	---	---	1/957	---	---	17/957	11/957
	Control	---	---	---	0/785	---	---	7/785	2/785

Abbreviations: HIT=heparin-induced thrombocytopenia; IPC=intermittent pneumatic compression; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin

References for Evidence Tables

Barden B, Kröger K, Löer F. Intraoperative Dopplersonography of the femoral vein for maintenance of venous flow in a hip endoprosthesis. *Unfallchirurg* 2001;104:138-42.

Farag E, Dilger J, Brooks P, et al. Epidural analgesia improves early rehabilitation after total knee replacement. *J Clin Anesth* 2005;17:281-5. PMID: 15950853

Jorgensen LN, Rasmussen LS, Nielsen PT, et al. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. *Br J Anaesth* 1991;66:8-12. PMID: 1997063

Kim YH, Oh SH, Kim JS. Incidence and natural history of deep-vein thrombosis after total hip arthroplasty. A prospective and randomised clinical study. *J Bone Joint Surg Br* 2003;85:661-5. PMID: 12892186

Laupacis A, Rorabeck C, Bourne R, et al. The frequency of venous thrombosis in cemented and non-cemented hip arthroplasty. *J Bone Joint Surg Br* 1996;78:210-2. PMID: 8666626

Levy O, Martinowitz U, Oran A, et al. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. *J Bone Joint Surg Am* 1999;81:1580-8. PMID: 10565650

Mitchell D, Friedman RJ, Baker JD, 3rd, et al. Prevention of thromboembolic disease following total knee arthroplasty. Epidural versus general anesthesia. *Clin Orthop* 1991;(269):109-12. PMID: 1864027

Nielsen PT, Jorgensen LN, Albrecht-Beste E, et al. Lower thrombosis risk with epidural blockade in knee arthroplasty. *Acta Orthop Scand* 1990;61:29-31. PMID: 2186591

Pitto RP, Hamer H, Fabiani R, et al. Prophylaxis against fat and bone-marrow embolism during total hip arthroplasty reduces the incidence of postoperative deep-vein thrombosis: a controlled, randomized clinical trial. *J Bone Joint Surg Am* 2002;84-A:39-48. PMID: 11792778

Planes A, Samama MM, Lensing AW, et al. Prevention of deep vein thrombosis after hip replacement--comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost* 1999;81:22-5. PMID: 10348714

Thorey F, Stukenborg-Colsman C, Windhagen H, et al. The effect of tourniquet release timing on perioperative blood loss in simultaneous bilateral cemented total knee arthroplasty: A prospective randomized study. *Technology and Health Care* 2008;16:85-92. PMID: 18487854

Westrich GH, Winiarsky R, Betsy M, et al. Effect on deep venous thrombosis with flexion during total knee arthroplasty. *HSS Journal* 2006;2:148-53. PMID: 18751828

Williams-Russo P, Sharrock NE, Haas SB, et al. Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. *Clin Orthop* 1996;:199-208. PMID: 8895639

Abdel-Salam A, Eyres K. Effects of tourniquet during total knee arthroplasty: A prospective randomised study. *J Bone Joint Surg* 1995;77-B:250-3. PMID: 7706340

McKenzie PJ, Wishart HY, Gray I, et al. Effects of anaesthetic technique on deep vein thrombosis. A comparison of subarachnoid and general anaesthesia. *Br J Anaesth* 1985;57:853-7. PMID: 4027101

Wakankar HM, Nicholl JE, Koka R, et al. The tourniquet in total knee arthroplasty. *J Bone Joint Surg* 1999;81-B:30-3. PMID: 10067997

Modig J, Hjelmstedt A, Sahlstedt B, et al. Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. *Acta Chir Scand* 1981;147:125-30. PMID: 7324741

Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986;56:53-6. PMID: 3535158

Chin PL, Amin MS, Yang KY, et al. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised

controlled trial. *J Orthop Surg* 2009;17:1-5. PMID: 19398783

Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *J Bone Joint Surg Br* 1992;74:45-9. PMID: 1732264

Fuji T, Ochi T, Niwa S, et al. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. *J Orthop Sci* 2008;13:442-51. PMID: 18843459

Jorgensen PS, Knudsen JB, Broeng L, et al. [The thromboprophylactic effect of low molecular weight heparin (Fragmin) in hip fracture surgery. A placebo controlled trial]. *Ugeskr Laeger* 1993;155:706-8. PMID: 8384388

Jorgensen PS, Knudsen JB, Broeng L, et al. The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. *Clin Orthop* 1992;(278):95-100. PMID: 1314147

Kim YH, Choi IY, Park MR, et al. Prophylaxis for deep vein thrombosis with aspirin or low molecular weight dextran in Korean patients undergoing total hip replacement. A randomized controlled trial. *Int Orthop* 1998;22:6-10. PMID: 9549575

Lassen MR, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthop Scand* 1991;62:33-8. PMID: 1848385

McKenna R, Galante J, Bachmann F, et al. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *Br Med J* 1980;280:514-7. PMID: 6989432

Samama CM, Clergue F, Barre J, et al. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. *Arar Study Group. Br J Anaesth* 1997;78:660-5. PMID: 9215015

Sorensen JV, Borris LC, Lassen MR, et al. Levels of thrombin--antithrombin-III complex and factor VIII activity in relation to post-operative deep vein thrombosis and influence of prophylaxis with a low-

molecular-weight heparin. *Blood Coagul Fibrinolysis* 1990;1:389-92. PMID: 1966794

Sorensen JV, Borris LC, Lassen MR, et al. Association between plasma levels of tissue plasminogen activator and postoperative deep vein thrombosis--influence of prophylaxis with a low molecular weight heparin. The Venous Thrombosis Group. *Thromb Res* 1990;59:131-8. PMID: 2169077

Torholm C, Broeng L, Jorgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *J Bone Joint Surg Br* 1991;73:434-8. PMID: 1670445

Turpie AG. Enoxaparin prophylaxis in elective hip surgery. *Acta Chir Scand Suppl* 1990;556:103-7. PMID: 1963014

Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986;315:925-9. PMID: 3531851

WelinBerger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. *Acta Orthop Scand* 1982;53:937-45. PMID: 6184938

Wilson NV, Das SK, Kakkar VV, et al. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. *J Bone Joint Surg Br* 1992;74:50-2. PMID: 1732265

Warwick D, Bannister G, Glew D, et al. Perioperative low-Molecular-Weight Heparin: Is it effective and safe? *J Bone Joint Surg* 1995;77-B:715-9. PMID: 7559695

Fuji T, Fujita S, Ujihira T, et al. Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo. *J Arthroplasty* 2010;25:1267-74. PMID: 19854610

A multicenter, multinational, randomized double-blind comparison study of subcutaneous Org31540/SR90107A versus enoxaparin 40 mg o.d. in the prevention of deep vein thrombosis and symptomatic pulmonary embolism in hip fracture

surgery. (PENTHIFRA). Study No: EFC2698. GlaxoSmithKline Clinical Trial Register 2005;

Avikainen V, von Bonsdorff H, Partio E, et al. Low molecular weight heparin (enoxaparin) compared with unfractionated heparin in prophylaxis of deep venous thrombosis and pulmonary embolism in patients undergoing hip replacement. *Ann Chir Gynaecol* 1995;84:85-90. PMID: 7645915

Bailey JP, Kruger MP, Solano FX, et al. Prospective randomized trial of sequential compression devices vs low-dose warfarin for deep venous thrombosis prophylaxis in total hip arthroplasty. *J Arthroplasty* 1991;6:S29-35. PMID: 1774568

Barre J, Pfister G, Potron G, et al. [Comparison of the efficacy and tolerance of Kabi 2165 and standard heparin in the prevention of deep venous thrombosis in total hip prosthesis]. *J Mal Vasc* 1987;12:90-5. PMID: 2834500

Bonneux IM, Bellemans J, Fabry G. Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin. *Knee* 2006;13:118-21. PMID: 16387501

Cofrancesco E, Cortellaro M, Corradi A, et al. Coagulation activation markers in the prediction of venous thrombosis after elective hip surgery. *Thromb Haemost* 1997;77:267-9. PMID: 9157579

Colwell CW, Jr, Collis DK, Paulson R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. *J Bone Joint Surg Am* 1999;81:932-40. PMID: 10428124

Colwell CW, Jr, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. *J Bone Joint Surg Am* 1994;76:3-14. PMID: 8288662

Colwell CW, Jr, Spiro TE, Trowbridge AA, et al. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty.

Enoxaparin Clinical Trial Group. *Clin Orthop* 1995;(321):19-27. PMID: 7497668

Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989;19:5-12. PMID: 2537787

Eriksson BI, Bauer KA, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001;345:1298-304. PMID: 11794148

Eriksson BI, Dahl OE, Buller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005;3:103-11. PMID: 15634273

Eriksson BI(a), Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5:2178-85. PMID: 17764540

Eriksson BI(b), Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949-56. PMID: 17869635

Eriksson BI, Ekman S, Kalebo P, et al. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. *Lancet* 1996;347:635-9. PMID: 8596376

Eriksson BI (a), Ekman S, Lindbratt S, et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* 1997;79:326-33. PMID: 9070519

Eriksson BI, Eriksson E, Risberg B. Impaired fibrinolysis and postoperative thromboembolism in orthopedic patients. *Thromb Res* 1991;62:55-64. PMID: 1853306

Eriksson BI, Kalebo P, Anthymyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. *J Bone Joint Surg Am* 1991;73:484-93. PMID: 2013587

Eriksson BI, Kalebo P, Risberg B. Clinical experience of a low molecular weight heparin (Fragmin) in the prevention of thromboembolism after total hip replacement. *Semin Thromb Hemost* 1993;19:122-7. PMID: 8395714

Eriksson BI (b), Wille-Jorgensen P, Kalebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* 1997;337:1329-35. PMID: 9358126

Fauno P, Suomalainen O, Rehnberg V, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. *J Bone Joint Surg Am* 1994;76:1814-8. PMID: 7989386

Fitzgerald RH,Jr, Spiro TE, Trowbridge AA, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J Bone Joint Surg Am* 2001;83-A:900-6. PMID: 11407799

Francis CW, Pellegrini VD,Jr, Marder VJ, et al. Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992;267:2911-5. PMID: 1583760

Francis CW, Pellegrini VD,Jr, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. *J Bone Joint Surg Am* 1997;79:1365-72. PMID: 9314399

Greinacher A, Eichler P, Albrecht D, et al. Antihirudin antibodies following low-dose subcutaneous treatment with desirudin for thrombosis prophylaxis after hip-replacement surgery: incidence and clinical relevance. *Blood* 2003;101:2617-9. PMID: 12393696

Haas SB, Insall JN, Scuderi GR, et al. Pneumatic sequential-compression boots compared with aspirin

prophylaxis of deep-vein thrombosis after total knee arthroplasty. *J Bone Joint Surg Am* 1990;72:27-31. PMID: 2404020

Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993;329:1370-6. PMID: 8413432

Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients a double-blind, randomized comparisons. *Arch Intern Med* 2000;160:2199-207. PMID: 10904464

Kennedy JG, Soffe KE, Rogers BW, et al. Deep vein thrombosis prophylaxis in hip fractures: A comparison of the arteriovenous impulse system and aspirin. *Journal of Trauma - Injury, Infection and Critical Care* 2000;48:268-72. PMID: 10697085

Lassen M, Bauer K, Eriksson B, et al. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002;359:1715-20. PMID: 12049858

Lassen MR, Davidson BL, Gallus A, et al. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007;5:2368-75. PMID: 17868430

Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Ann Intern Med* 1996;124:619-26. PMID: 8607589

Levine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991;114:545-51. PMID: 1848054

Levine MN, Planes A, Hirsh J, et al. The relationship between anti-factor Xa level and clinical outcome in patients receiving enoxaparine low molecular weight heparin to prevent deep vein thrombosis after hip replacement. *Thromb Haemost* 1989;62:940-4. PMID: 2556813

Lotke PA, Palevsky H, Keenan AM, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop* 1996;:251-8. PMID: 8595765

Menzin J, Richner R, Huse D, et al. Prevention of deep-vein thrombosis following total hip replacement surgery with enoxaparin versus unfractionated heparin: a pharmacoeconomic evaluation. *Ann Pharmacother* 1994;28:271-5. PMID: 8173149

Palement G, Wessinger SJ, Waltman AC, et al. Low-dose warfarin versus external pneumatic compression for prophylaxis against venous thromboembolism following total hip replacement. *J Arthroplasty* 1987;2:23-6. PMID: 3572408

Planes A, Vochelle N, Mazas F, et al. [Double-blind randomized comparative study of enoxaparin and standard heparin in the prevention of thromboembolic disease during insertion of total hip replacement]. *Rev Med Interne* 1988;9:327-33. PMID: 2841742

Planes A, Vochelle N, Mazas F, et al. [The use of enoxaparine in preventing deep venous thrombosis following total hip prosthesis. Randomized multicenter prospective trial]. *Rev Chir Orthop Reparatrice Appar Mot* 1988;74:215-8. PMID: 2852830

Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost* 1988;60:407-10. PMID: 2853459

RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9. PMID: 18534438

Santori FS, Vitullo A, Stopponi M, et al. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Joint Surg Br* 1994;76:579-83. PMID: 8027144

Schwartzmann CR, Cavalieri CR, Drumond SN, et al. Randomized, comparative, open study to assess the efficacy and safety of enoxaparin compared with

unfractionated heparin in the prophylaxis of venous thromboembolism in patients undergoing total hip arthroplasty. *Revista Brasileira De Ortopedia* 1996;31:797-808. PMID: Embase 1996366023

Senaran H, Acaroglu E, Ozdemir HM, et al. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. *Arch Orthop Trauma Surg* 2006;126:1-5. PMID: 16333632

Stone MH, Limb D, Campbell P, et al. A comparison of intermittent calf compression and enoxaparin for thromboprophylaxis in total hip replacement. A pilot study. *Int Orthop* 1996;20:367-9. PMID: 9049766

Turpie AG, Bauer KA, Eriksson BI, et al. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002;359:1721-6. PMID: 12049860

Warkentin TE, Roberts RS, Hirsh J, et al. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch Intern Med* 2003;163:2518-24. PMID: 14609790

Warwick D, Harrison J, Glew D, et al. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *J Bone Joint Surg Am* 1998;80:1158-66. PMID: 9730125

Warwick D, Harrison J, Whitehouse S, et al. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. *J Bone Joint Surg Br* 2002;84:344-50. PMID: 12002490

Warkentin T, Levine M, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5. PMID: 7715641

Rader CP, Kramer C, König A, et al. Low-molecular-weight heparin and partial thromboplastin time-adjusted unfractionated heparin in thromboprophylaxis after total knee and total hip arthroplasty. *J arthroplasty* 1998;13:180-5. PMID: 9526211

Monreal M, Lafoz E, Navarro A, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *J Trauma* 1989;29:873-5. PMID: 2544742

Bauer KA, Eriksson BI, Lassen MR, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001;345:1305-10. PMID: 11794149

Dabigatran Etxilate vs Enoxaparin in Prevention of Venous Thromboembolism (VTE) Post Total Knee Replacement. Available at: <http://clinicaltrials.gov/ct2/show/NCT00152971>. Accessed Oct. 22, 2010.

Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. *Haemostasis* 1999;29:310-7. PMID: 10844404

Bara L, Planes A, Samama MM. Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery. *Br J Haematol* 1999;104:230-40. PMID: 10050702

Lachiewicz PF, Kelley SS, Haden LR. Two mechanical devices for prophylaxis of thromboembolism after total knee arthroplasty. A prospective, randomised study. *Journal of Bone and Joint Surgery - Series B* 2004;86:1137-41. PMID: 15568526

Planes A. An equivalence study of two low-molecular-weight heparins in the prevention and treatment of deep-vein thrombosis after total hip replacement. *Semin Thromb Hemost* 2000;26:57-60. PMID: 11011808

Ryan MG, Westrich GH, Potter HG, et al. Effect of mechanical compression on the prevalence of proximal deep venous thrombosis as assessed by magnetic resonance venography. *J Bone Joint Surg Am* 2002;84-A:1998-2004. PMID: 12429761

Silbersack Y, Taute BM, Hein W, et al. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in

combination with intermittent pneumatic compression. *J Bone Joint Surg Br* 2004;86:809-12. PMID: 15330019

Edwards JZ, Pulido PA, Ezzet KA, et al. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. *J Arthroplasty* 2008;23:1122-7. PMID: 18534421

Lieberman JR, Huo MM, Hanway J, et al. The prevalence of deep venous thrombosis after total hip arthroplasty with hypotensive epidural anesthesia. *J Bone Joint Surg Am* 1994;76:341-8. PMID: 8126039

Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. *J Bone Joint Surg Am* 1996;78:826-34. PMID: 8666599

Woolson ST, Watt JM. Intermittent pneumatic compression to prevent proximal deep venous thrombosis during and after total hip replacement. A prospective, randomized study of compression alone, compression and aspirin, and compression and low-dose warfarin. *J Bone Joint Surg Am* 1991;73:507-12. PMID: 2013589

Andersen BS. Postoperative activation of the haemostatic system--influence of prolonged thromboprophylaxis in patients undergoing total hip arthroplasty. *Haemostasis* 1997;27:219-27. PMID: 9690480

Arnesen H, Dahl OE, Aspelin T, et al. Sustained prothrombotic profile after hip replacement surgery: the influence of prolonged prophylaxis with dalteparin. *J Thromb Haemost* 2003;1:971-5. PMID: 12871363

Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996;335:696-700. PMID: 8703168

Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. *J Bone Joint Surg Am* 2001;83-A:336-45. PMID: 11263636

Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery--results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost* 1997;77:26-31. PMID: 9031444

Dahl OE, Aspelin T, Arnesen H, et al. Increased activation of coagulation and formation of late deep venous thrombosis following discontinuation of thromboprophylaxis after hip replacement surgery. *Thromb Res* 1995;80:299-306. PMID: 8585042

Eriksson BI, Lassen MR, PENTasaccharide in Hip-FRActure Surgery Plus, Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2003;163:1337-42. PMID: 12796070

Manganelli D, Pazzagli M, Mazzantini D, et al. Prolonged prophylaxis with unfractionated heparin is effective to reduce delayed deep vein thrombosis in total hip replacement. *Respiration* 1998;65:369-74. PMID: 9782219

Nilsson PE, Bergqvist D, Benoni G, et al. The postdischarge prophylactic management of the orthopedic patient with low-molecular-weight heparin: enoxaparin. *Orthopedics* 1997;20:22-5. PMID: 9048404

Planes A, Vochelle N. The post-hospital discharge venous thrombosis risk of the orthopedic patient. *Orthopedics* 1997;20:18-21. PMID: 9048403

Planes A, Vochelle N, Darmon JY. Out-of-hospital prophylaxis with low-molecular-weight heparin in hip surgery: the French study--venographic outcome at 35 days. *Chest* 1998;114:125S-9S. PMID: 9726707

Planes A, Vochelle N, Darmon JY, et al. Efficacy and safety of postdischarge administration of enoxaparin in the prevention of deep venous thrombosis after total hip replacement. A prospective randomised double-blind placebo-controlled trial. *Drugs* 1996;52:47-54. PMID: 9042560

Planes A, Vochelle N, Darmon JY, et al. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin

versus placebo. *Lancet* 1996;348:224-8. PMID: 8684199

Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med* 2002;162:1966-71. PMID: 12230419

Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Arch Intern Med* 1989;149:771-4. PMID: 2650646

Kalodiki EP, Hoppensteadt DA, Nicolaides AN, et al. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *Int Angiol* 1996;15:162-8. PMID: 8803642

Stannard JP, Harris RM, Bucknell AL, et al. Prophylaxis of deep venous thrombosis after total hip arthroplasty by using intermittent compression of the plantar venous plexus. *Am J Orthop* 1996;25:127-34. PMID: 8640382

Dorr LD, Gendelman V, Maheshwari AV, et al. Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. *J Bone Joint Surg Am* 2007;89:2648-57. PMID: 18056497

Gandhi R, Razak F, Tso P, et al. Metabolic syndrome and the incidence of symptomatic deep vein thrombosis following total knee arthroplasty. *J Rheumatol* 2009;36:2298-301. PMID: 19684153

Leizorovicz A, Turpie AGG, Cohen AT, et al. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART Study. *Journal of Thrombosis and Haemostasis* 2005;3:28-34. PMID: 15634263

Lemos MJ, Sutton D, Hozack WJ, et al. Pulmonary embolism in total hip and knee arthroplasty. Risk factors in patients on warfarin prophylaxis and analysis of the prothrombin time as an indicator of warfarin's prophylactic effect. *Clin Orthop* 1992;:158-63. PMID: 1516307

McNamara I, Sharma A, Prevost T, et al. Symptomatic venous thromboembolism following a

hip fracture. *Acta Orthop* 2009;80:687-92. PMID: 19968601

Ryan DH, Crowther MA, Ginsberg JS, et al. Relation of factor V Leiden genotype to risk for acute deep venous thrombosis after joint replacement surgery. *Ann Intern Med* 1998;128:270-6. PMID: 9471929

Haas SB, Tribus CB, Insall JN, et al. The significance of calf thrombi after total knee arthroplasty. *J Bone Joint Surg Br* 1992;74:799-802. PMID: 1447236

Lieberman JR, Wollaeger J, Dorey F, et al. The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. *J Bone Joint Surg Am* 1997;79:319-25. PMID: 9070518

Cusick LA, Beverland DE. The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. *J Bone Joint Surg Br* 2009;91:645-8. PMID: 19407300

Happe LE, Farrelly EM, Stanford RH, et al. Cost and occurrence of thrombocytopenia in patients receiving venous thromboembolism prophylaxis following major orthopaedic surgeries. *J Thromb Thrombolysis* 2008;26:125-31. PMID: 18034323

Sachs RA, Smith JH, Kuney M, et al. Does anticoagulation do more harm than good? A

comparison of patients treated without prophylaxis and patients treated with low-dose warfarin after total knee arthroplasty. *J Arthroplasty* 2003;18:389-95. PMID: 12820078

Shorr AF, Kwong LM, Sarnes M, et al. Venous thromboembolism after orthopedic surgery: implications of the choice for prophylaxis. *Thromb Res* 2007;121:17-24. PMID: 17449088

Bozic KJ, Vail TP, Pekow PS, et al. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? *J Arthroplasty* 2010;25:1053-60. PMID: 19679434

Froimson MI, Murray TG, Fazekas AF. Venous thromboembolic disease reduction with a portable pneumatic compression device. *J Arthroplasty* 2009;24:310-6. PMID: 18534456

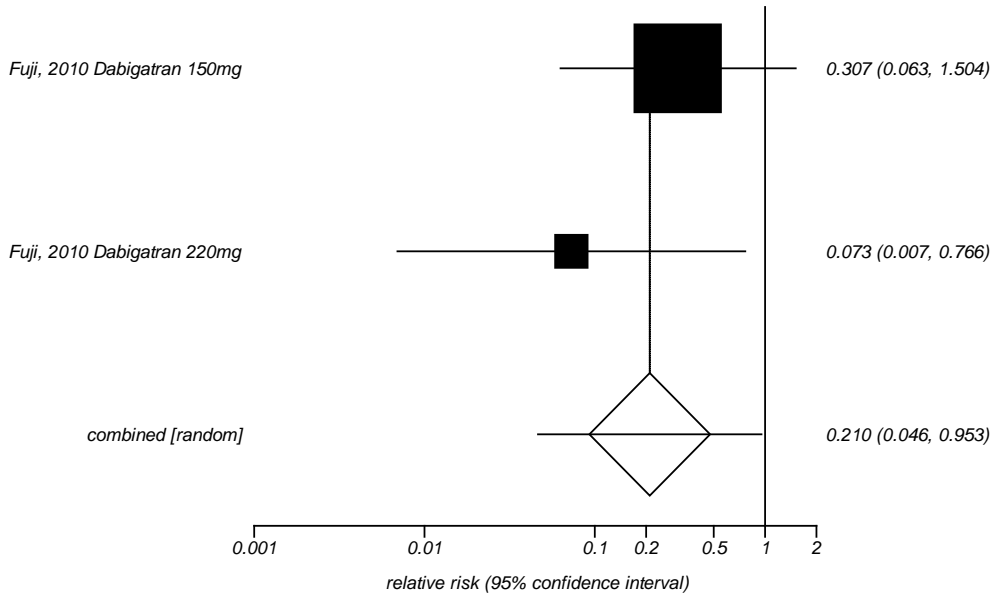
Gerkens S, Crott R, Closon MC, et al. Comparing the quality of care across Belgian hospitals from medical basic datasets: the case of thromboembolism prophylaxis after major orthopaedic surgery. *J Eval Clin Pract* 2010;16:685-692.

Yokote R, Matsubara M, Hirasawa, et al. Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population? *J Bone Joint Surg (Br)* 2011;93-B:251-256.

Appendix G. Forest Plots

Figure 1. Impact of pharmacologic prophylaxis versus no prophylaxis on major venous thromboembolism in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

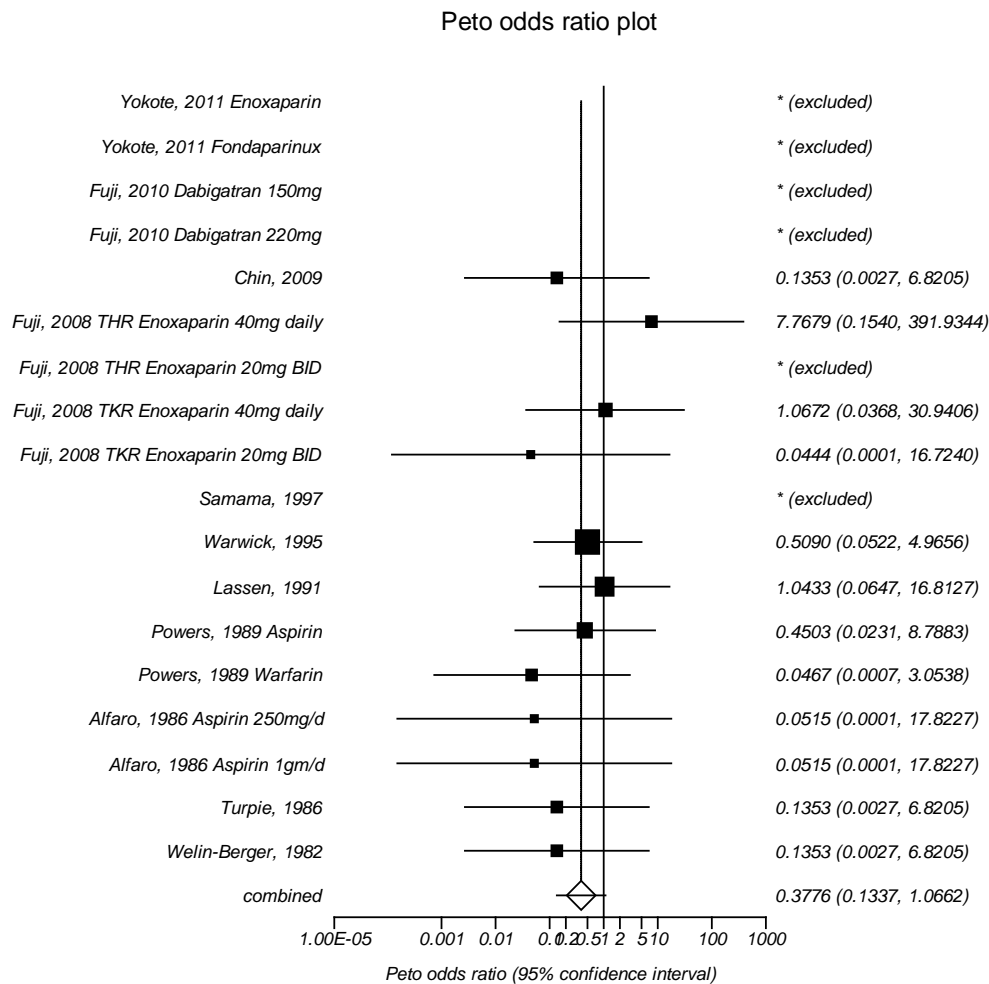


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

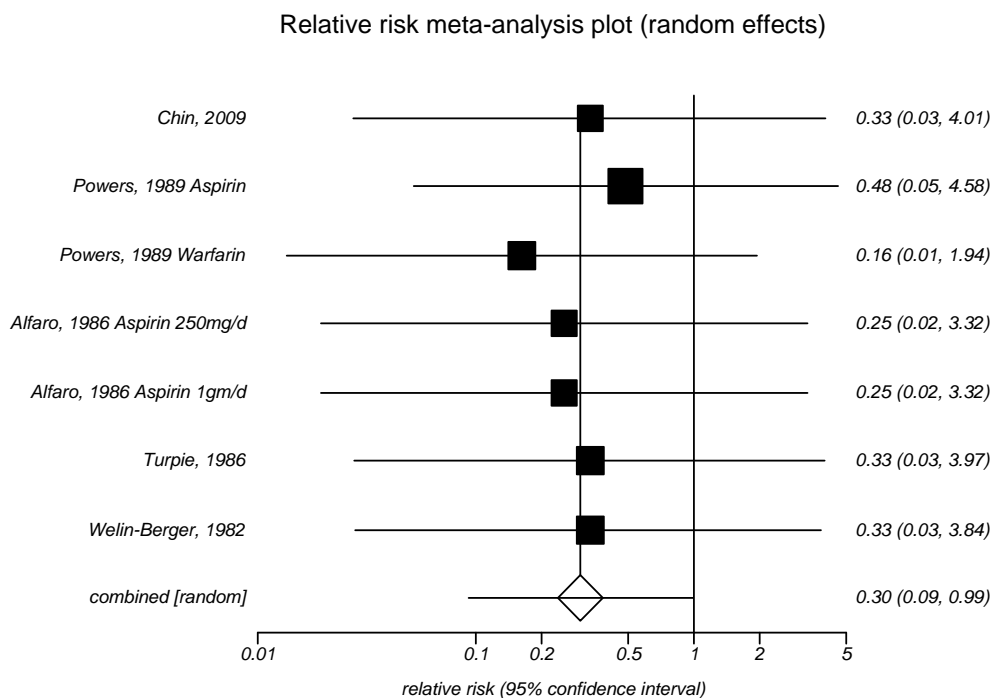
Figure 2. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.063

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

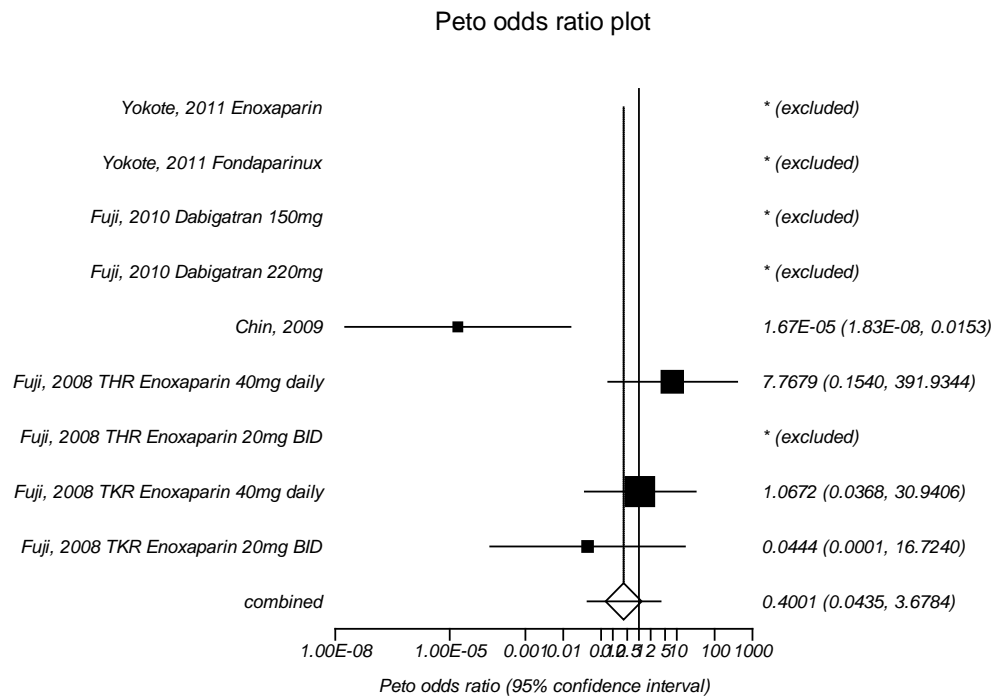
Figure 3. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

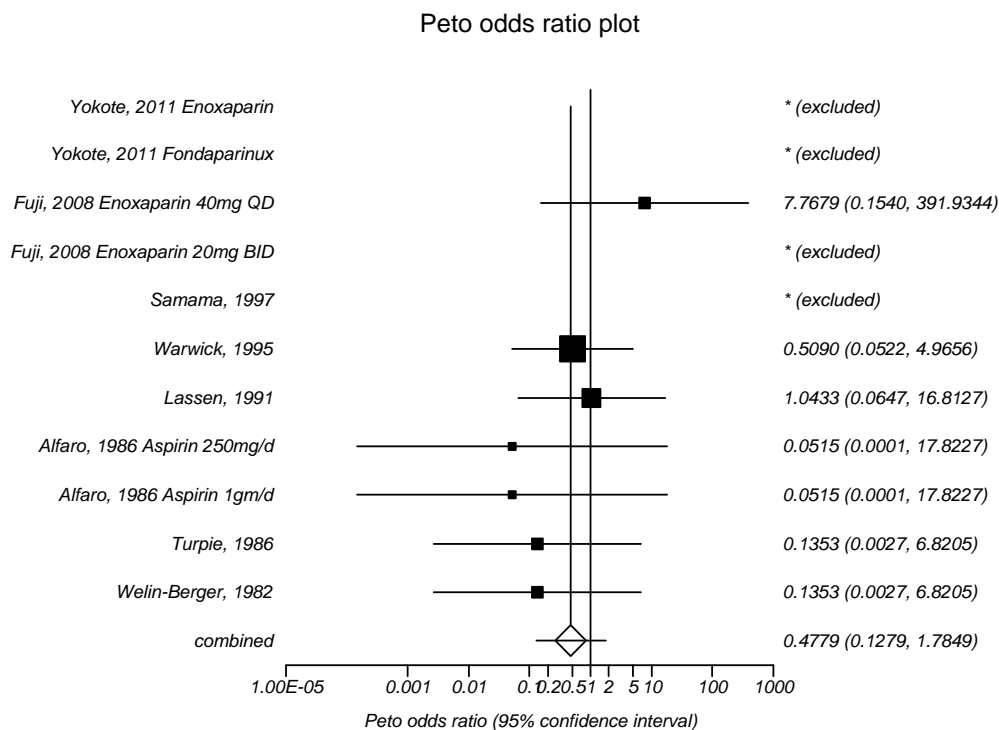
Figure 4. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 73.8 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

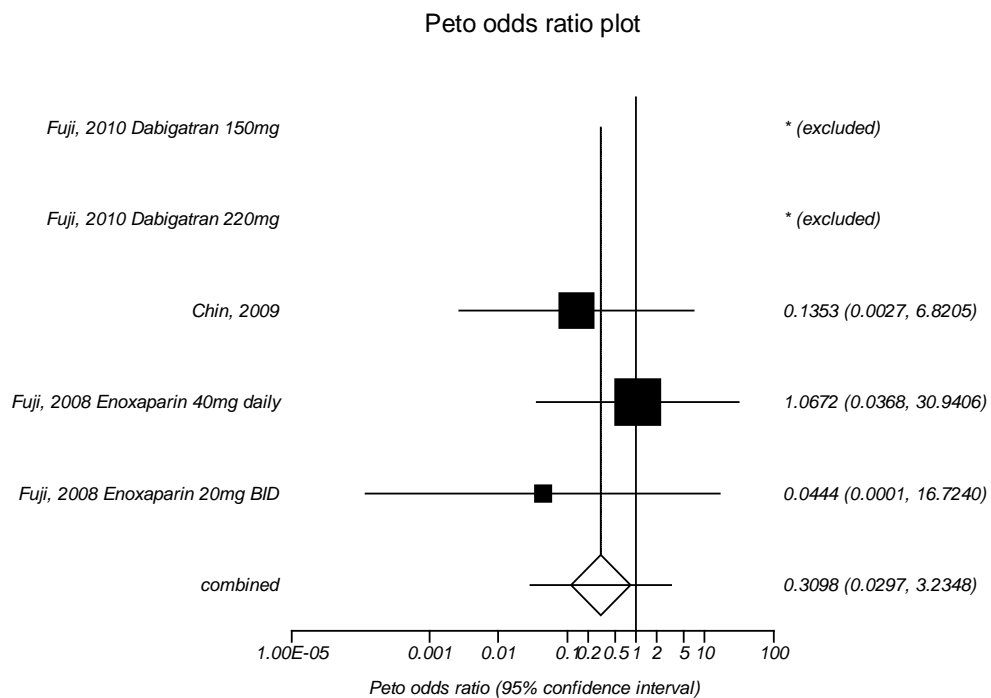
Figure 5. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 6. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited total knee replacement surgery

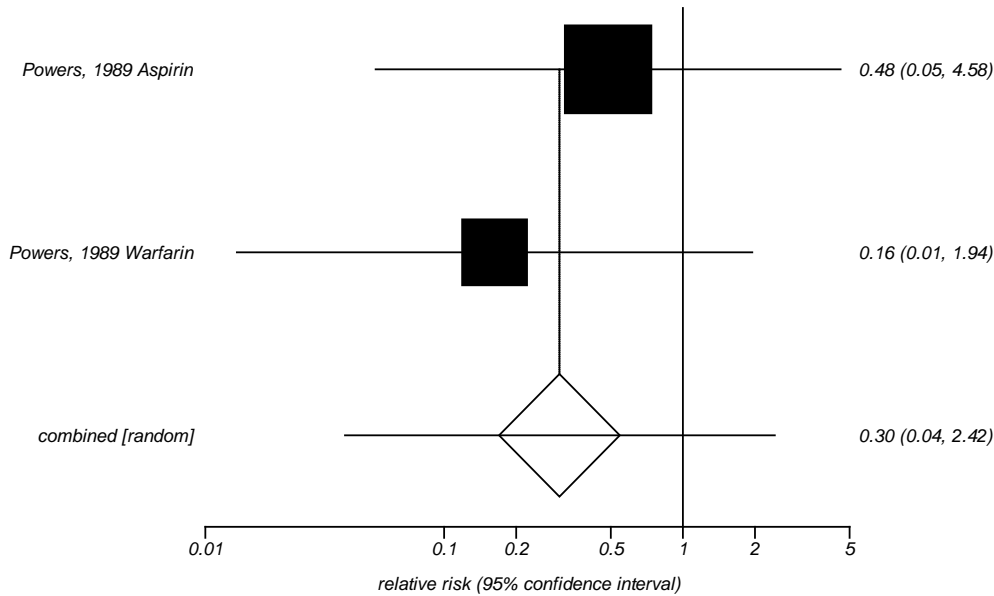


I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 7. Impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited hip fracture surgery

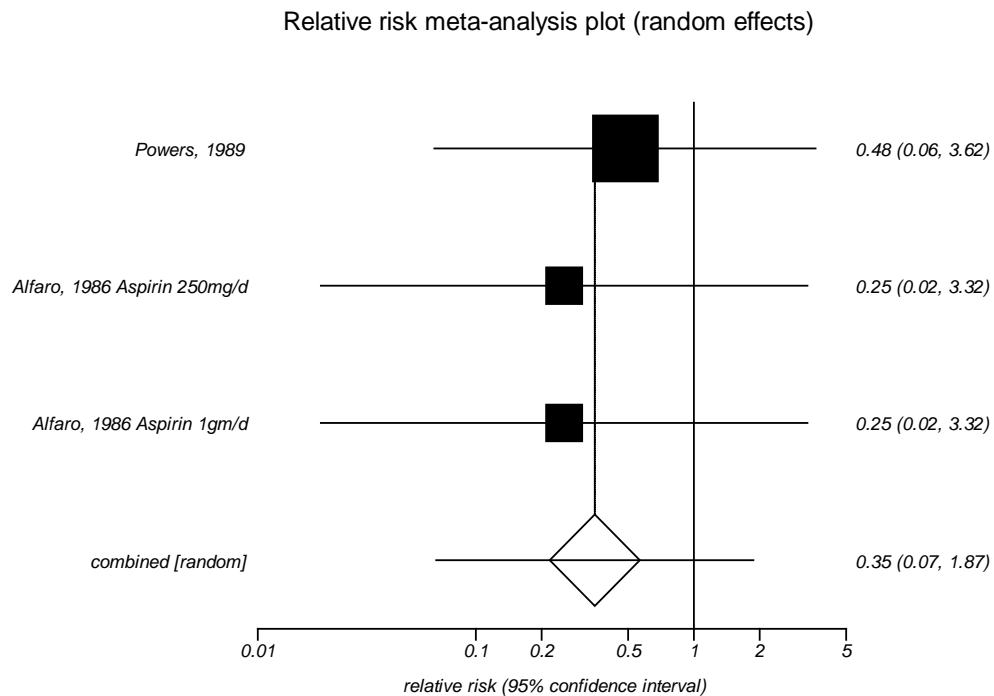
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

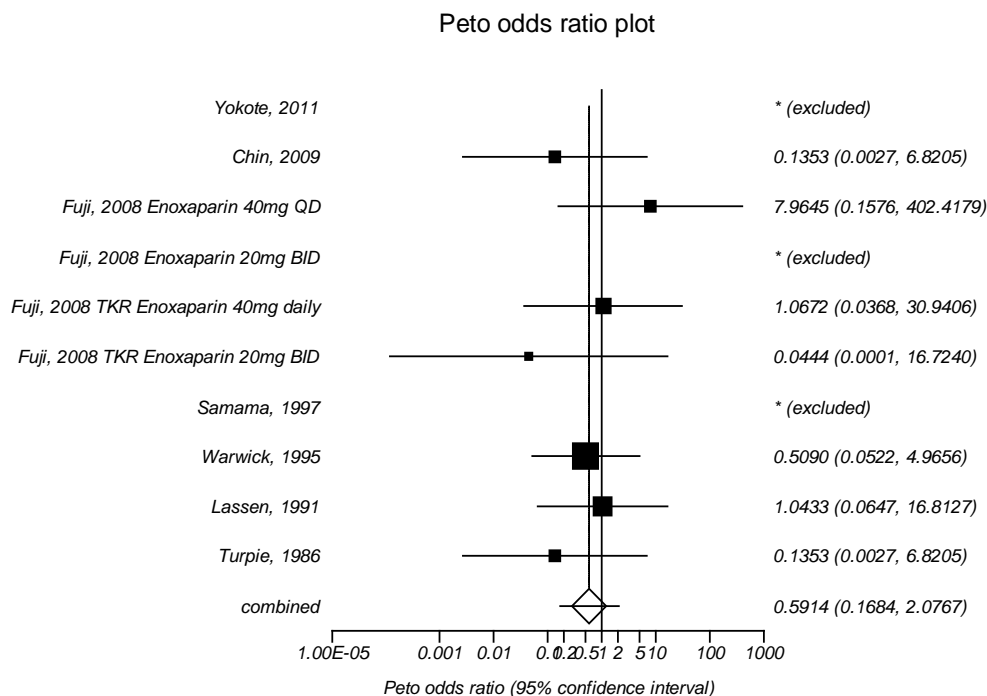
Figure 8. Impact of oral antiplatelet agents versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery



I^2 : 0 percent
 Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

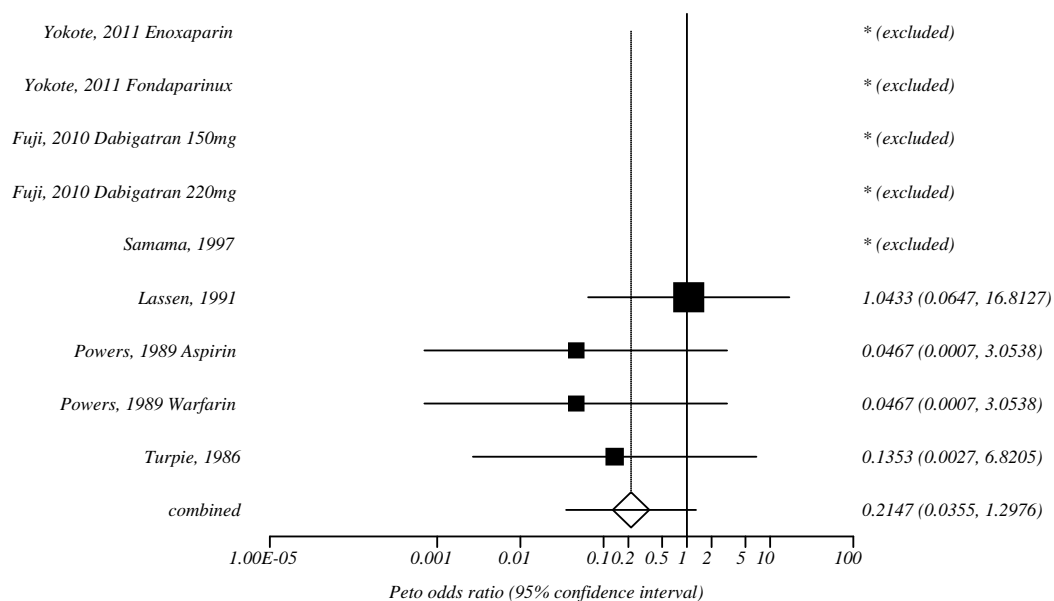
Figure 9. Impact of injectable low molecular weight heparins versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery



I^2 : 0 percent
 Egger's p-value: 0.511

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

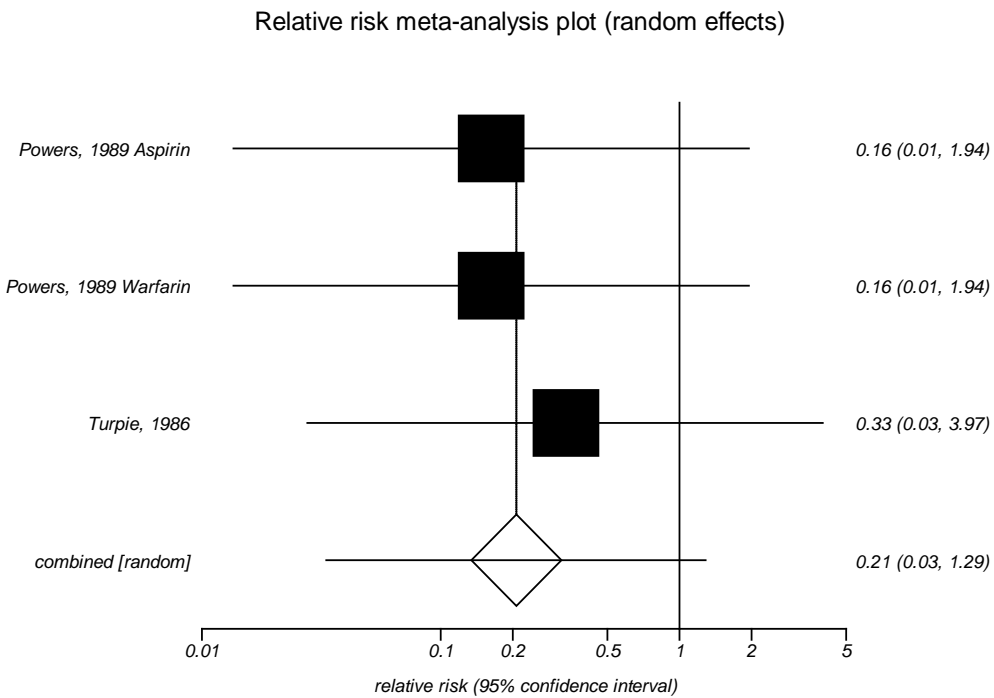
Figure 10. Impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery



I²: 0 percent
Egger's p-value: 0.009

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

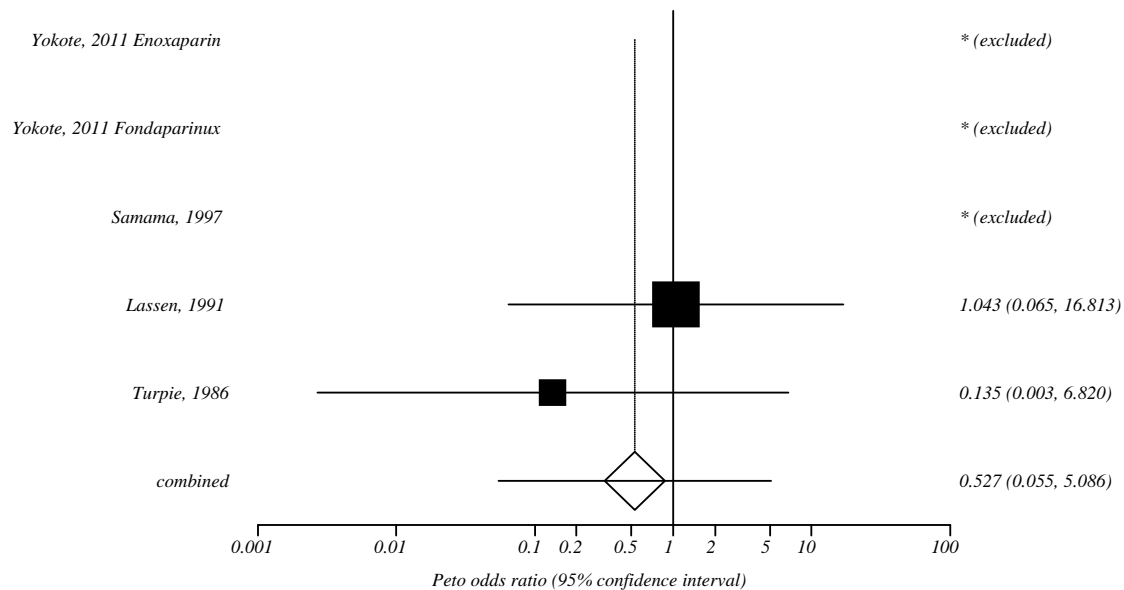
Figure 11. Impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 12. Impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery limited to total hip replacement



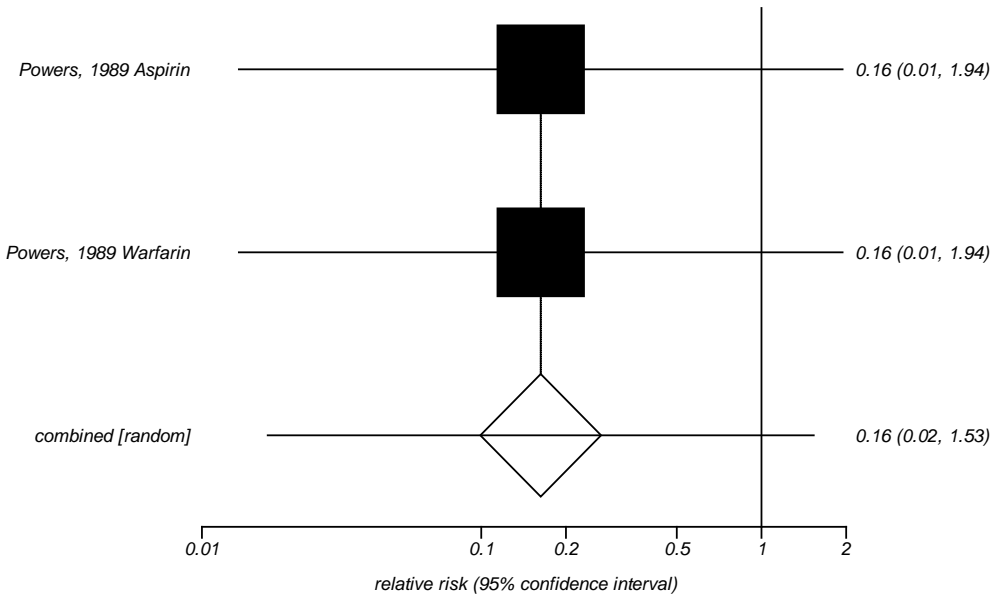
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 13. Impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery limited to hip fracture surgery

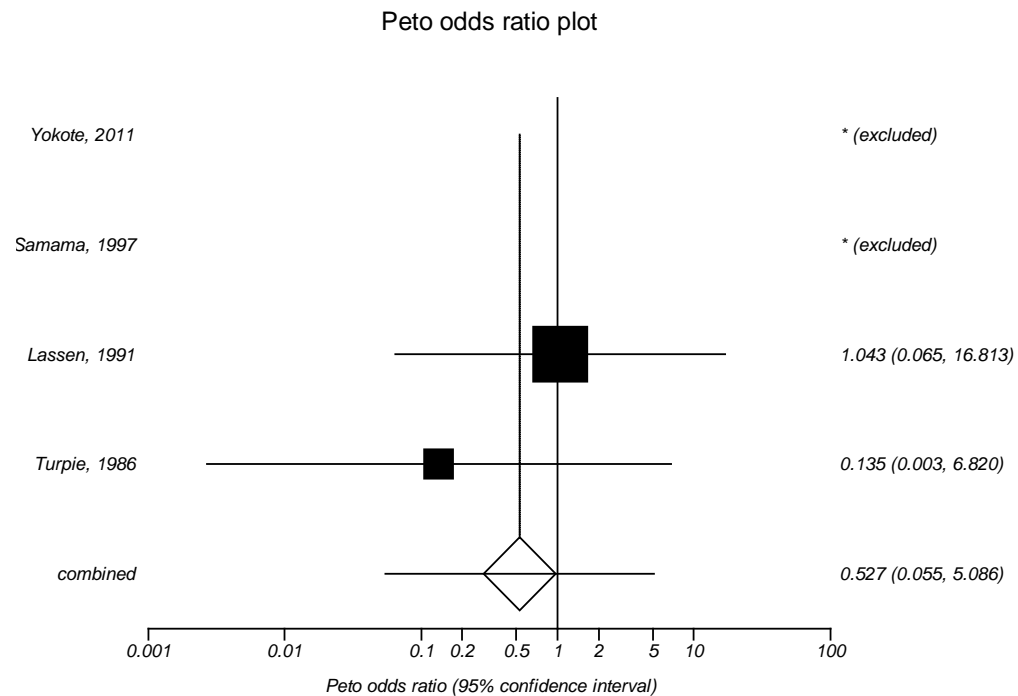
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

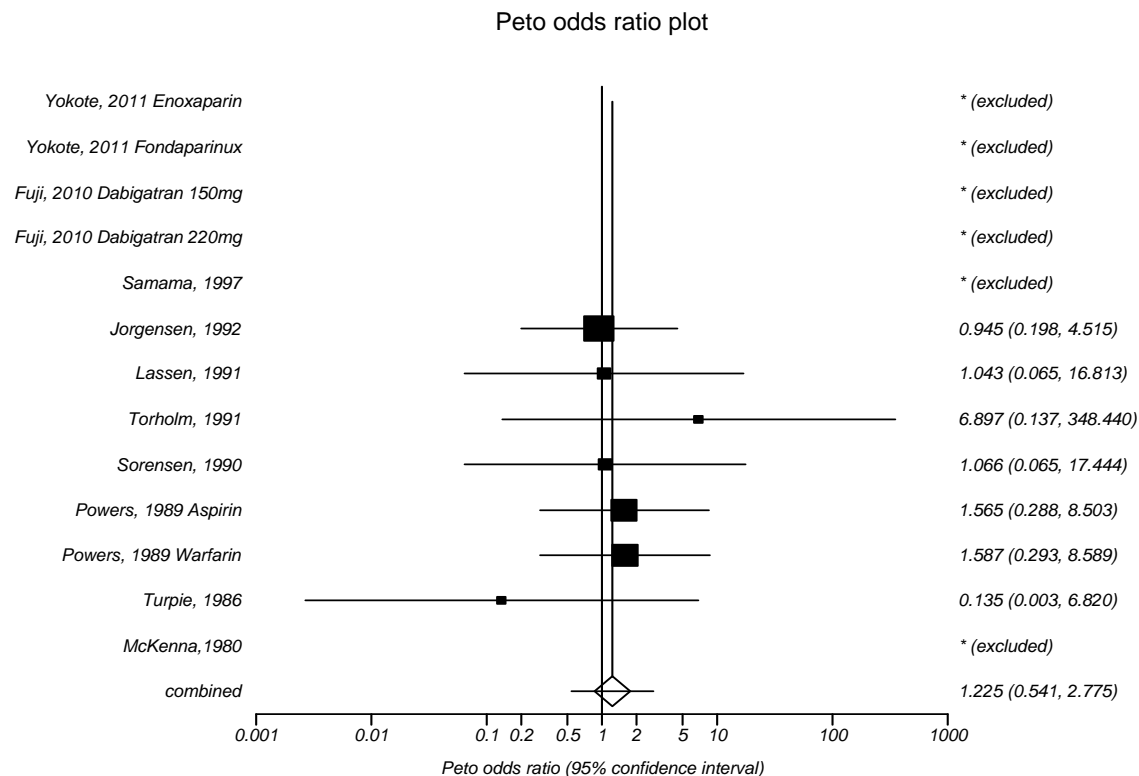
Figure 14. Impact of injectable low molecular weight heparins versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery



I²: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

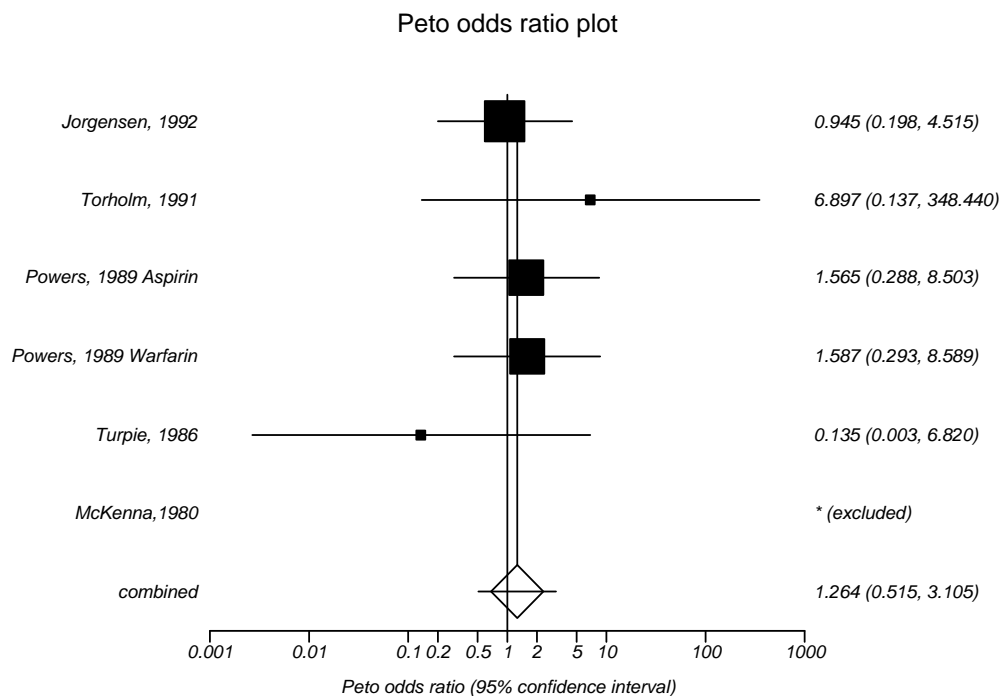
Figure 15. Impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.757

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

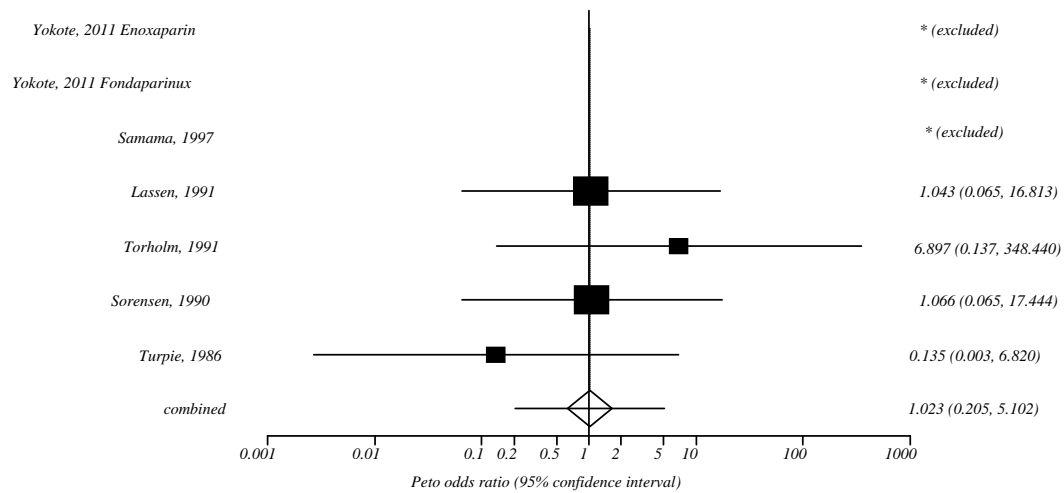
Figure 16. Impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

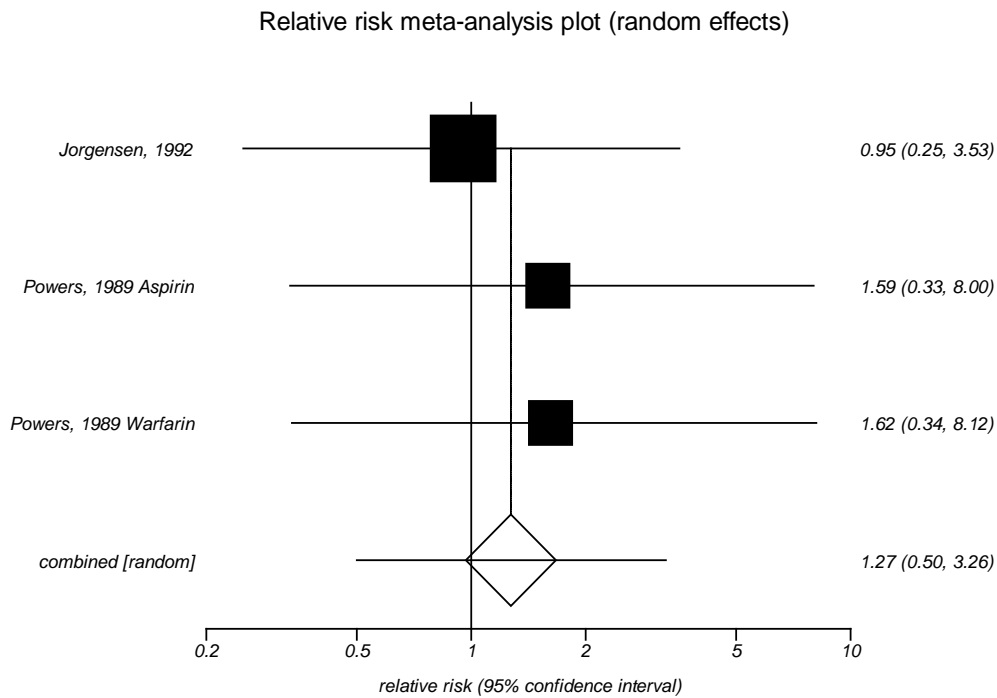
Figure 17. Impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

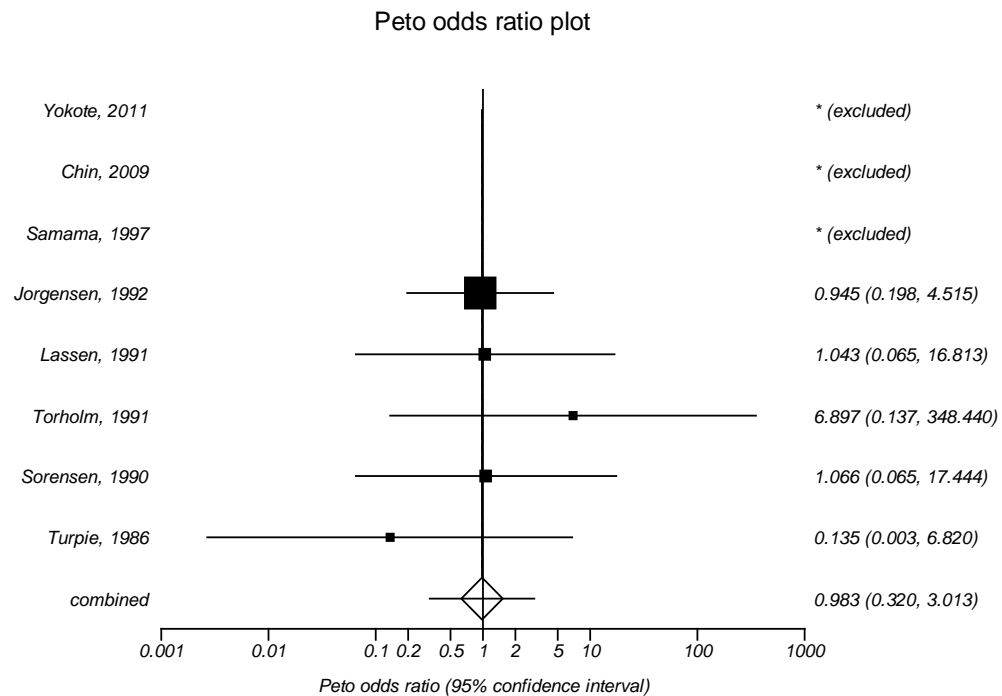
Figure 18. Impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery limited to hip fracture surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 19. Impact of injectable low molecular weight heparins versus no prophylaxis on mortality in patients who had major orthopedic surgery

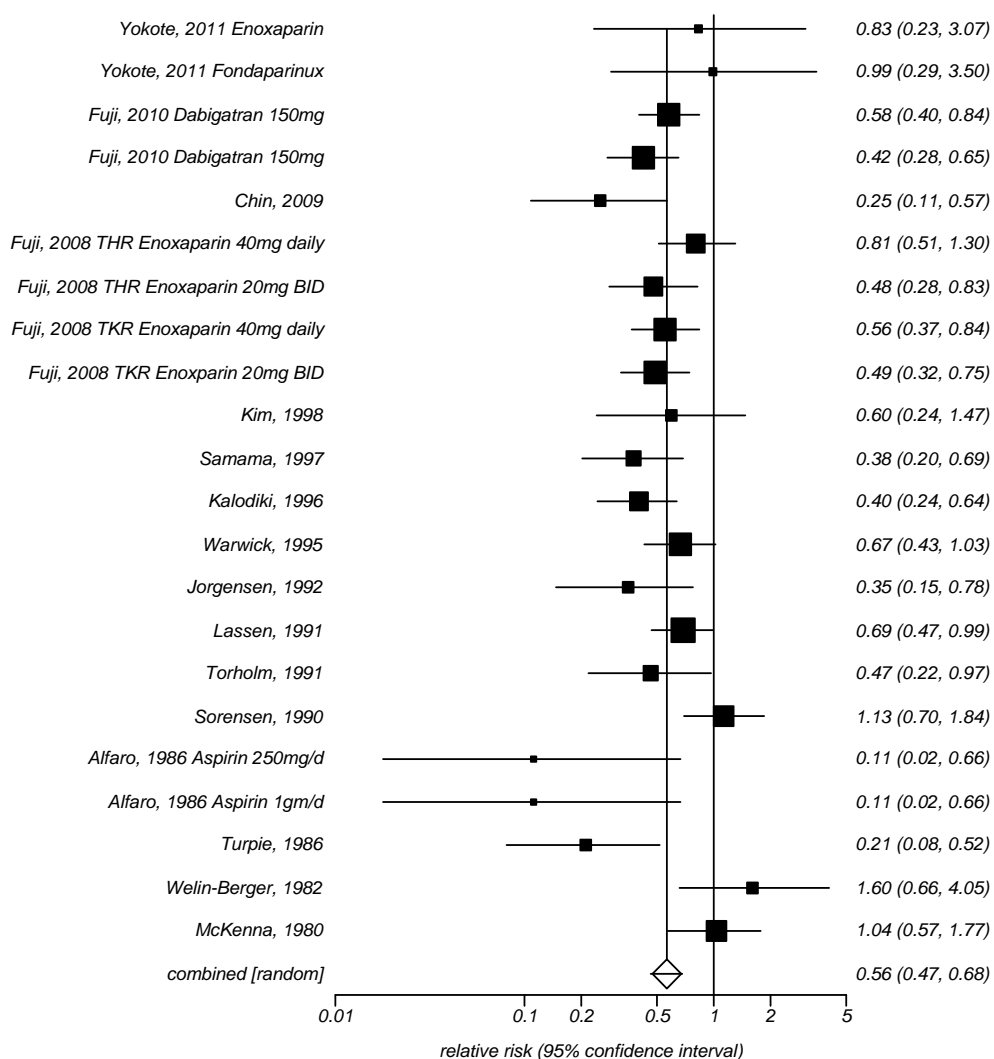


I^2 : 0 percent
 Egger's p-value: 0.962

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 20. Impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

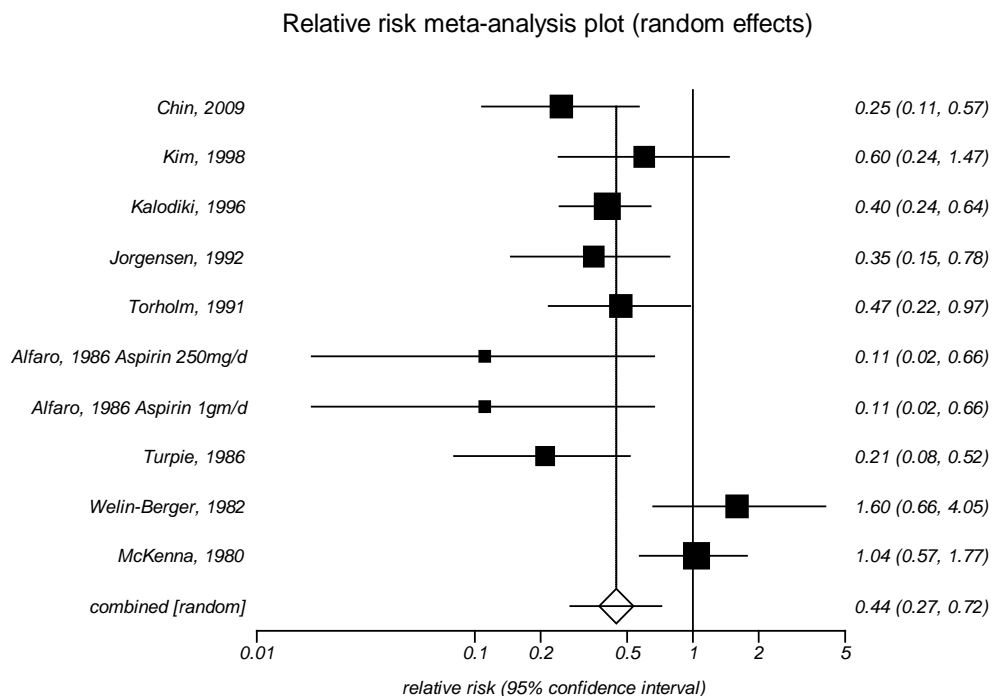


I^2 : 52.8 percent

Egger's p-value: 0.199

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

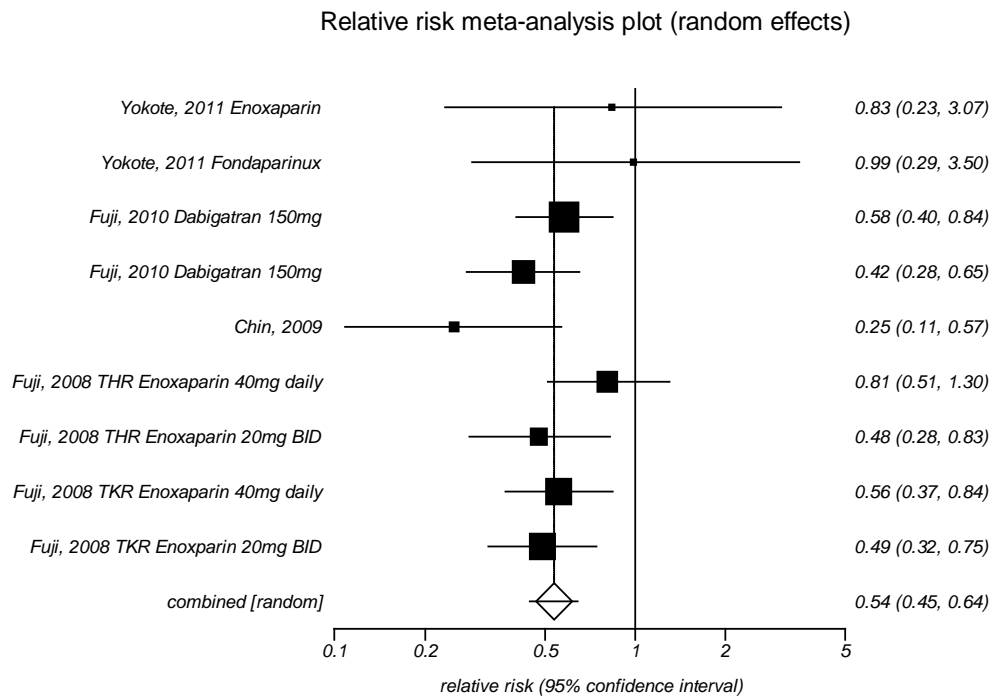
Figure 21. Impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I²: 69 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 22. Impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present

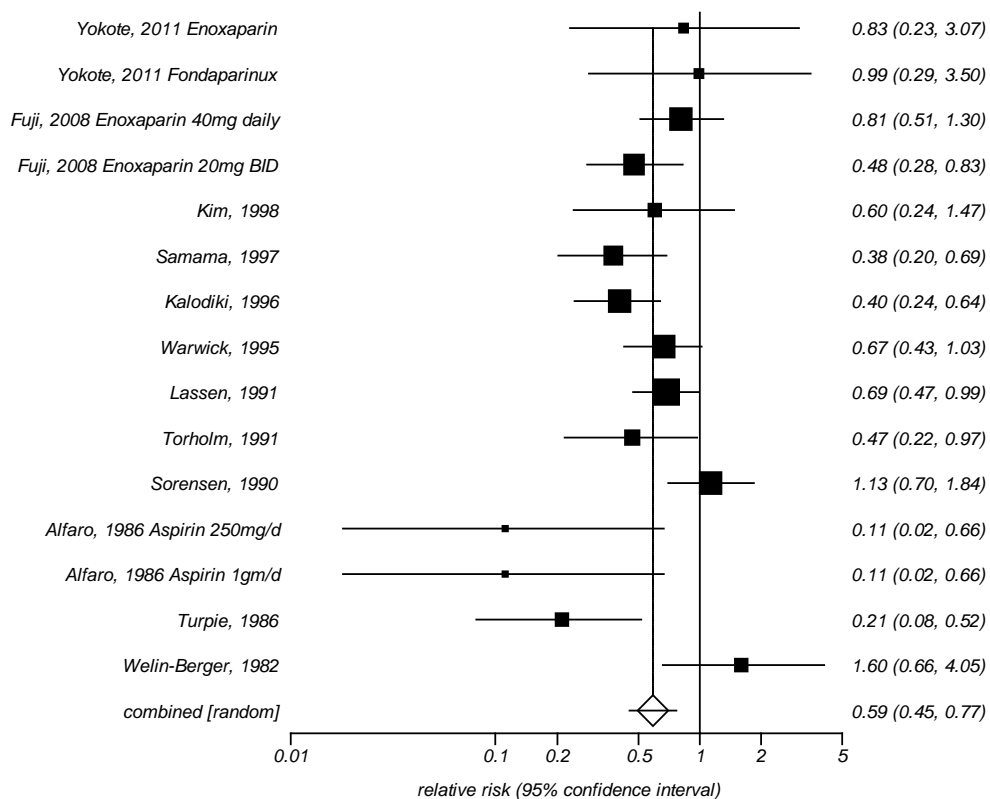


I²: 10.4 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 23. Impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement surgery

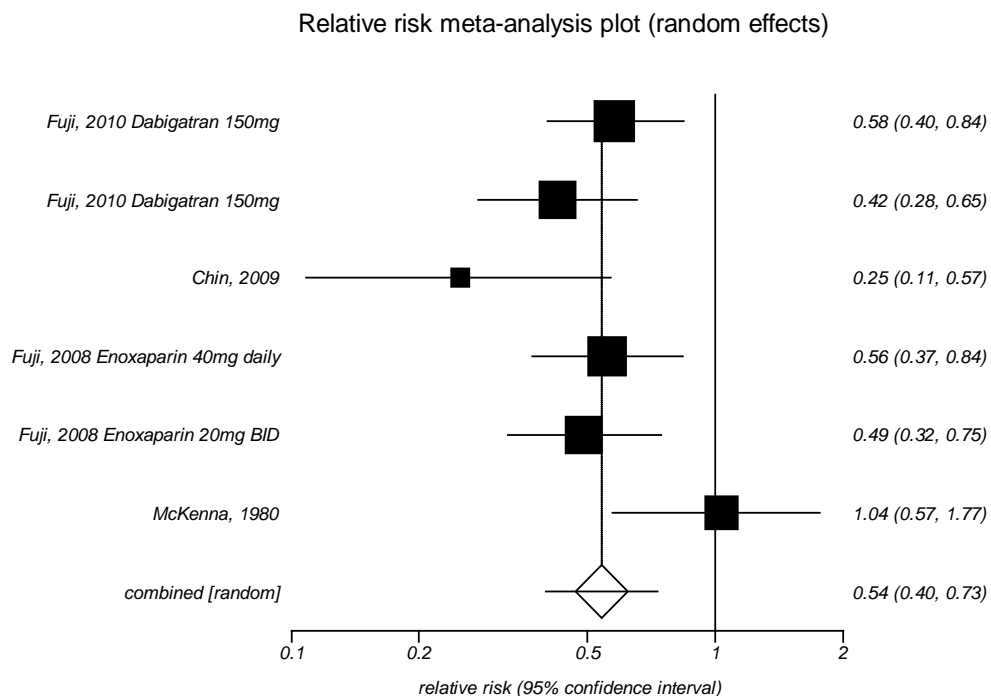
Relative risk meta-analysis plot (random effects)



I^2 : 52.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

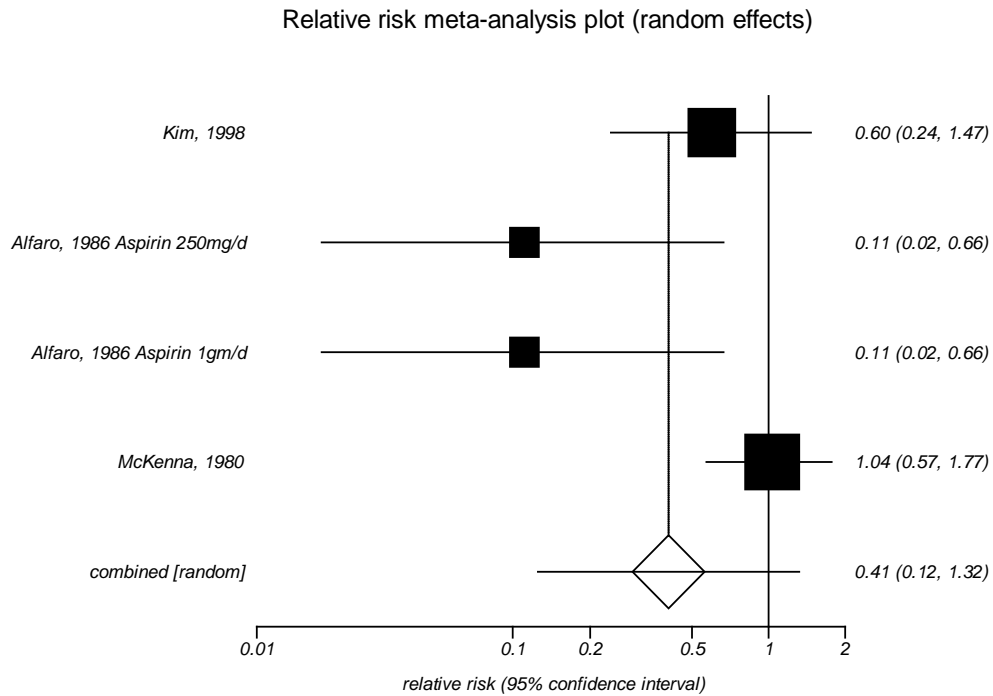
Figure 24. Impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to total knee replacement surgery



I^2 : 61.4 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 25. Impact of oral antiplatelet agents versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery

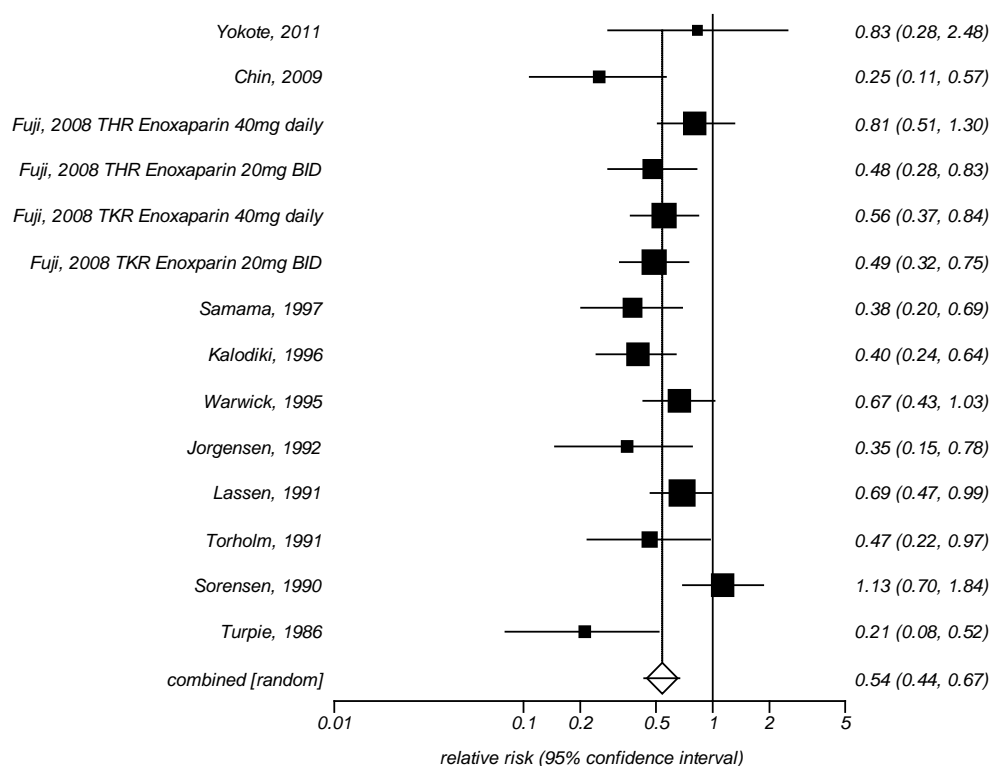


I^2 : 76 percent
 Egger's p-value: 0.002

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 26. Impact of injectable low molecular weight heparins versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery

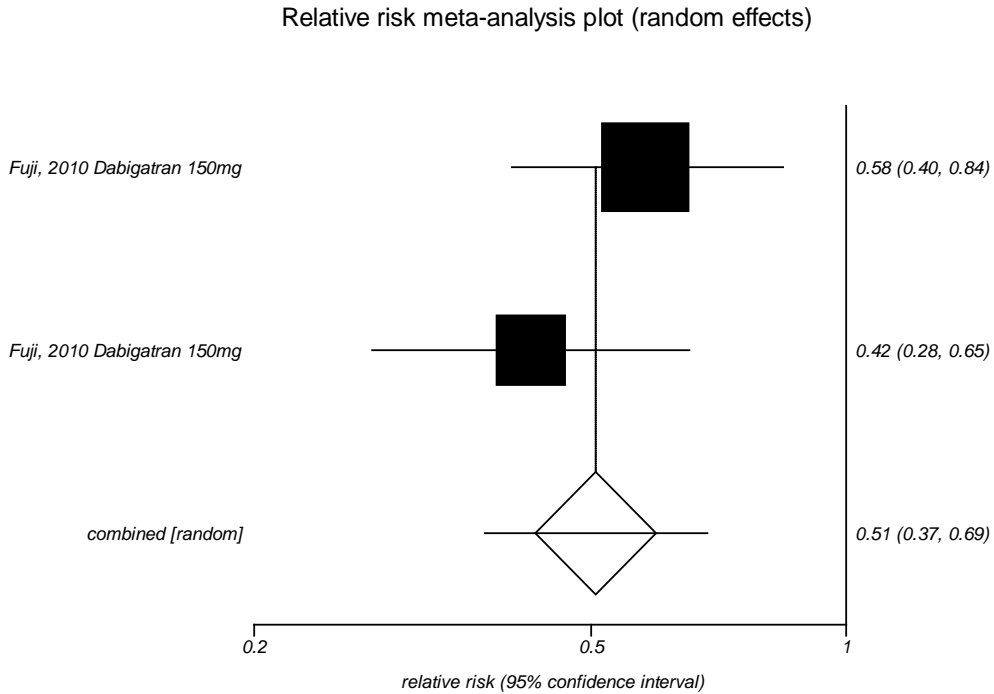
Relative risk meta-analysis plot (random effects)



I^2 : 50.2 percent
Egger's p-value: 0.088

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 27. Impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery

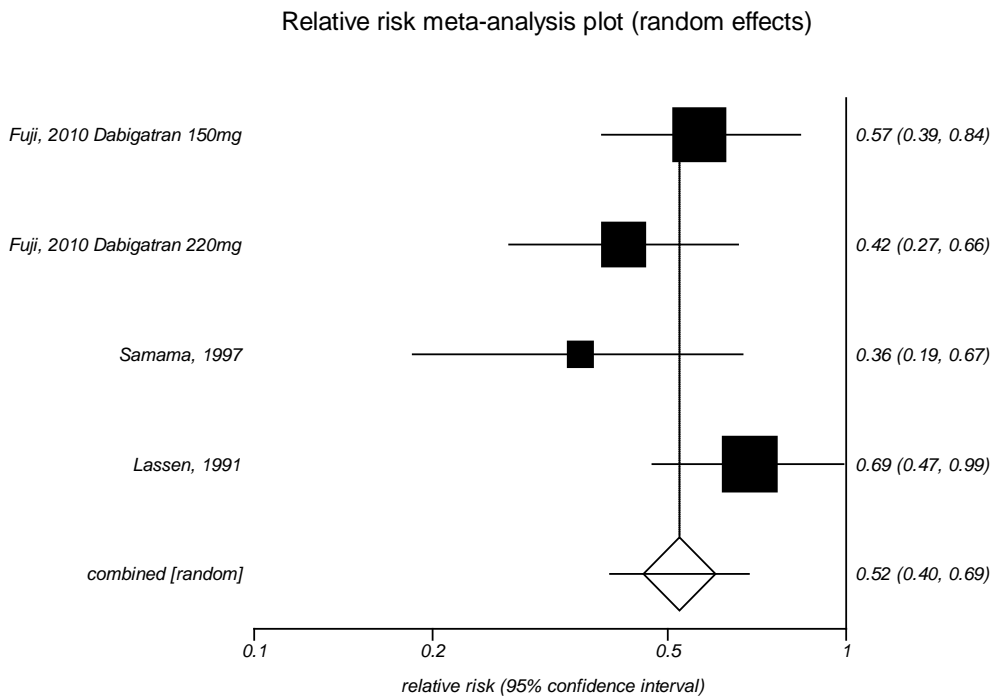


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

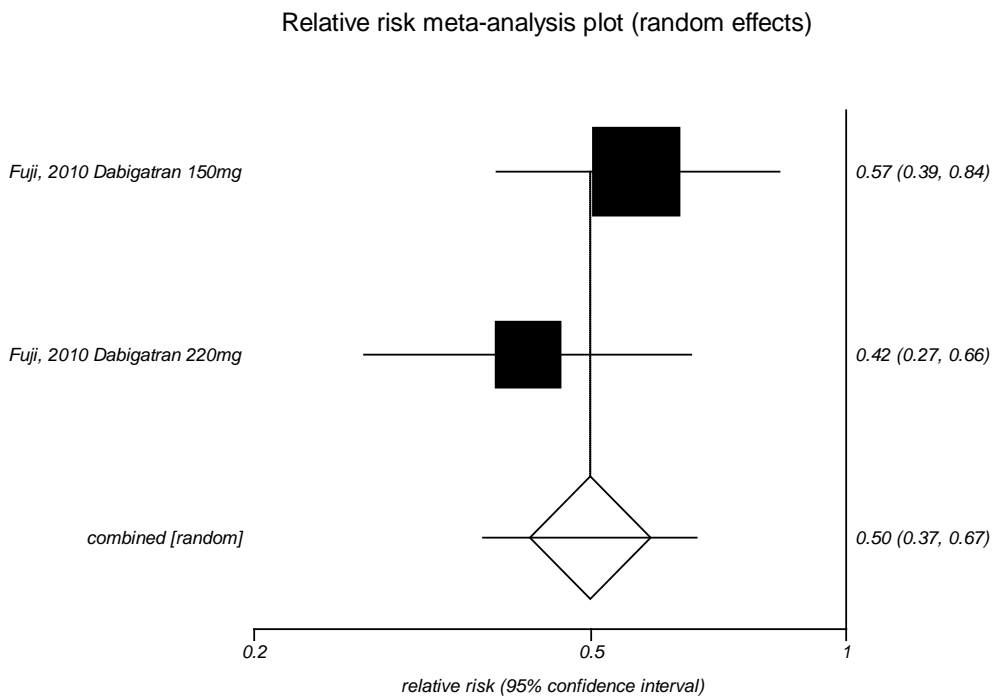
Figure 28. Impact of pharmacologic prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 32.7 percent
Egger's p-value: 0.168

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 29. Impact of pharmacologic prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present (same analysis as limited to total knee replacement; same analysis as injectable or oral direct thrombin inhibitors versus no prophylaxis in major orthopedic surgery)

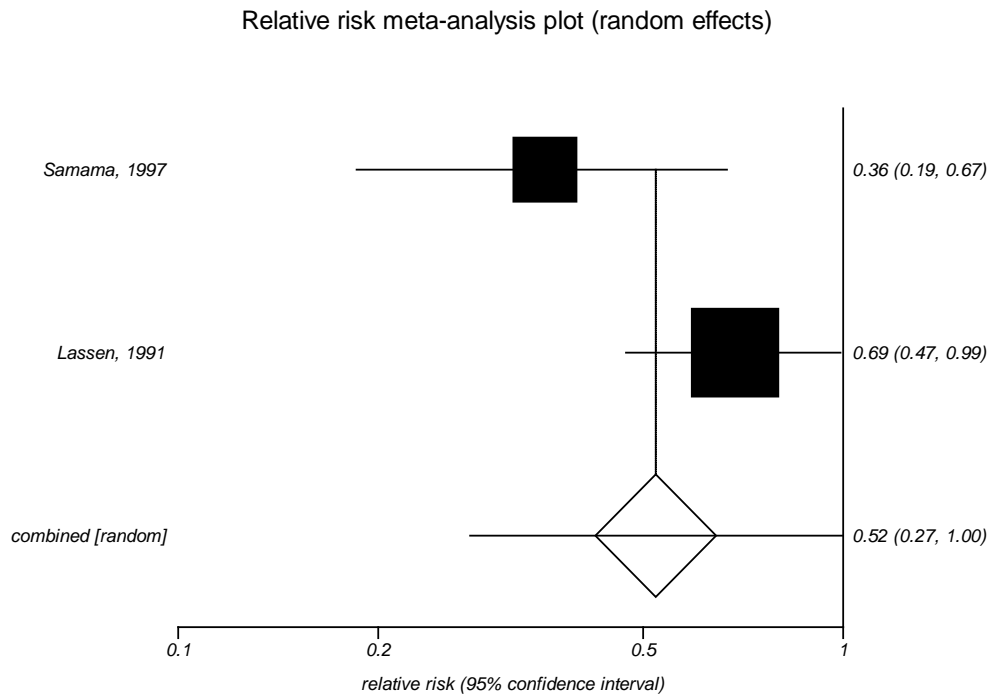


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 30. Impact of pharmacologic prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement (same analysis as low molecular weight heparin versus no prophylaxis in major orthopedic surgery)

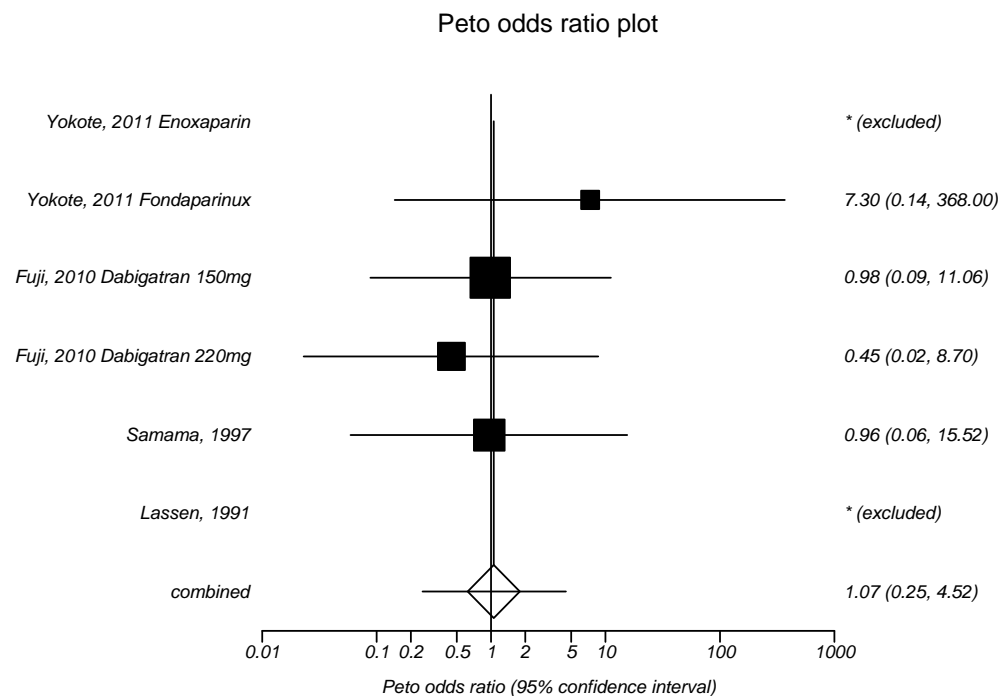


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

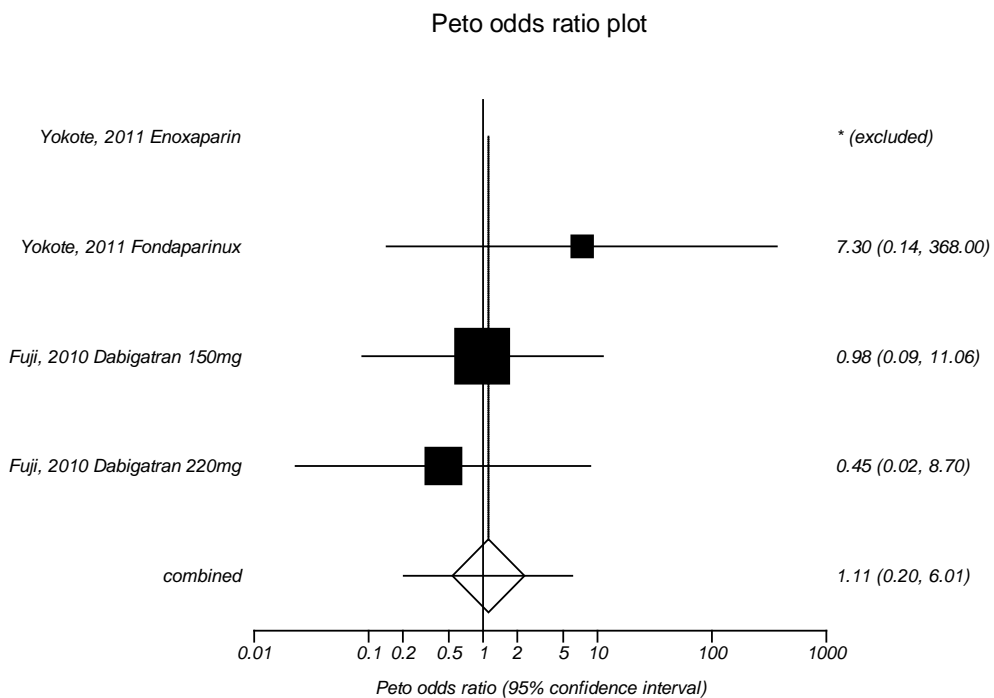
Figure 31. Impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.316

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

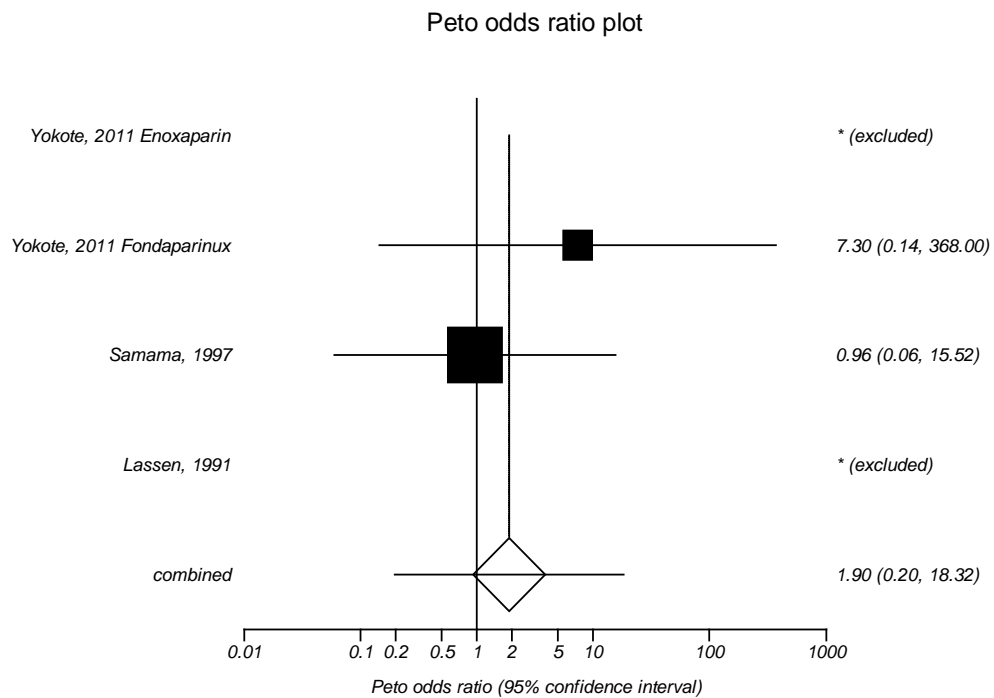
Figure 32. Impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to trials published in 2001-present



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

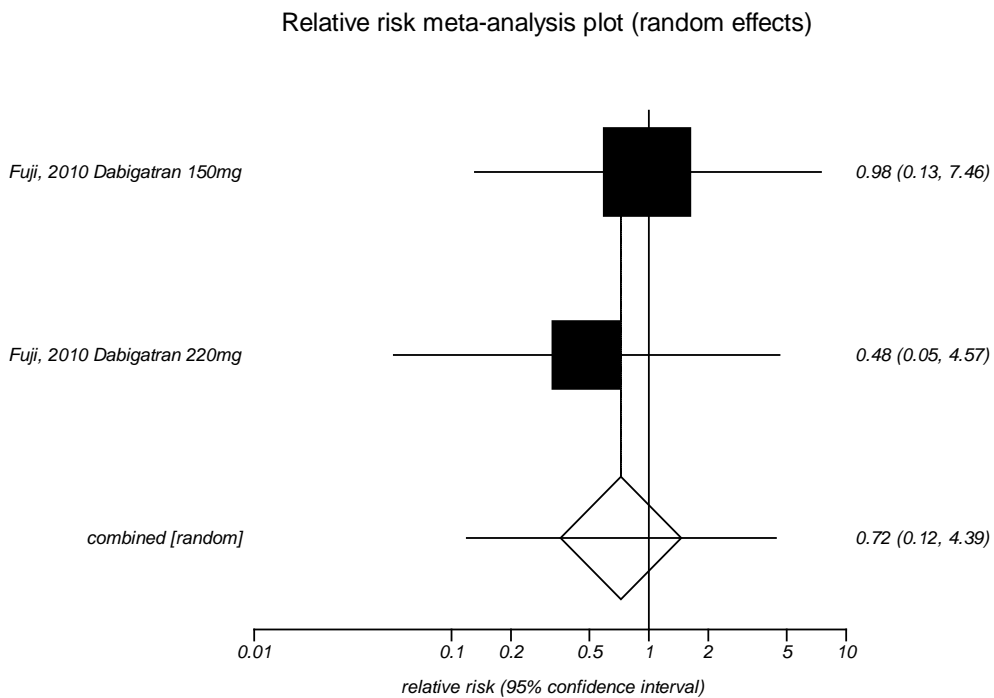
Figure 33. Impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to trials total hip replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

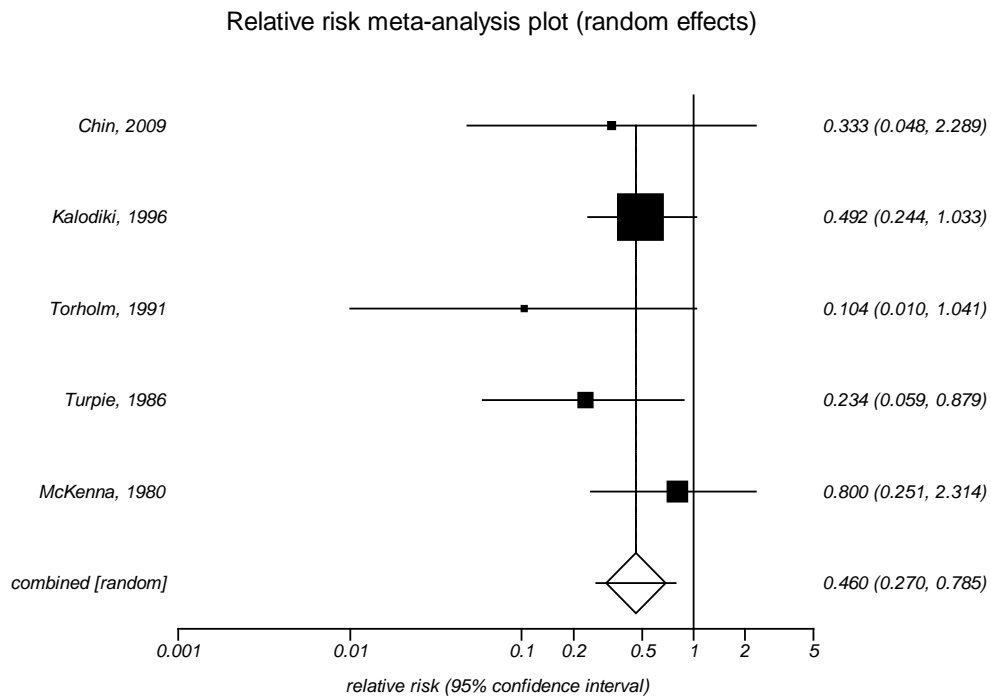
Figure 34. Impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to trials total knee replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

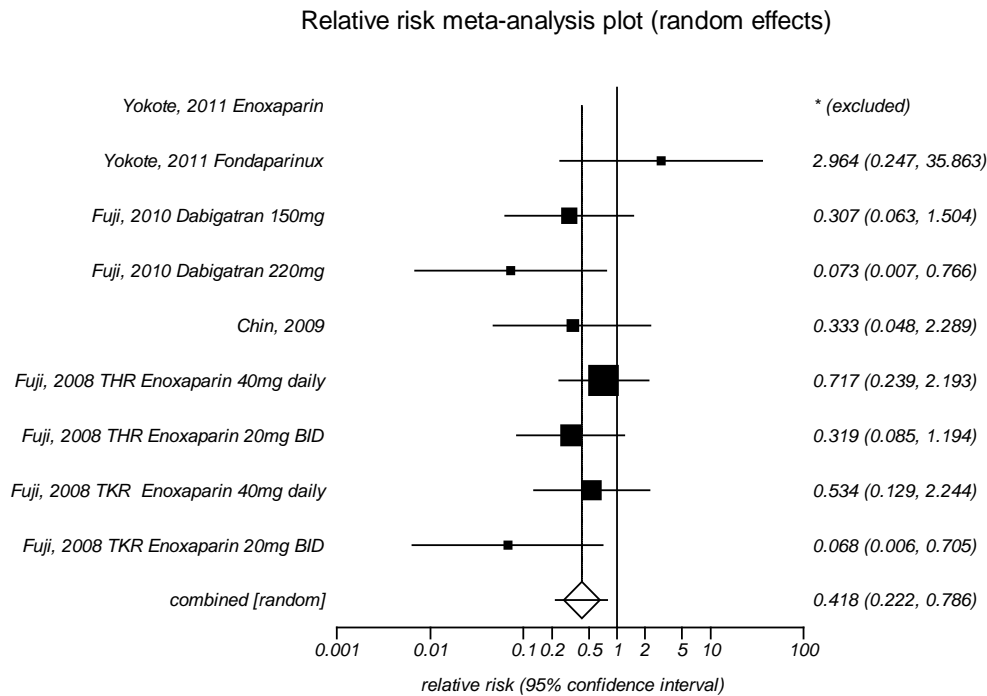
Figure 35. Impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 36. Impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present

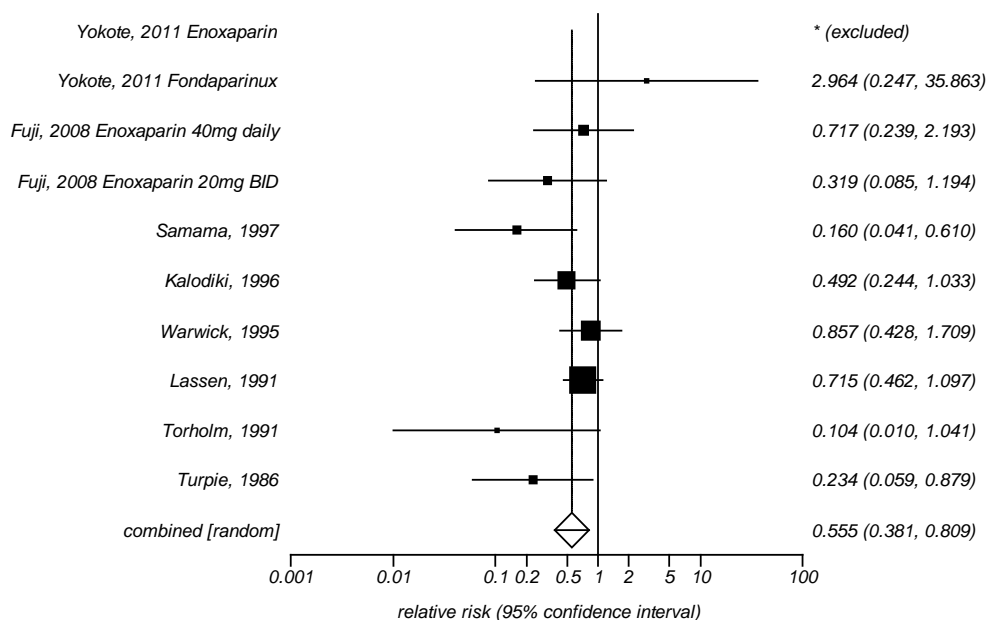


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 37. Impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement

Relative risk meta-analysis plot (random effects)

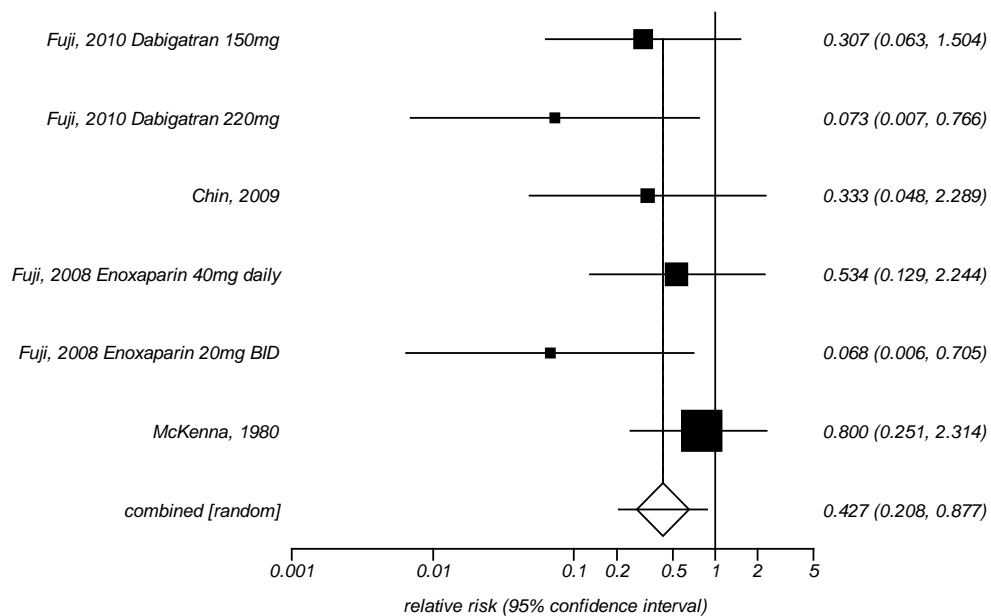


I^2 : 20.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 38. Impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited to total knee replacement

Relative risk meta-analysis plot (random effects)

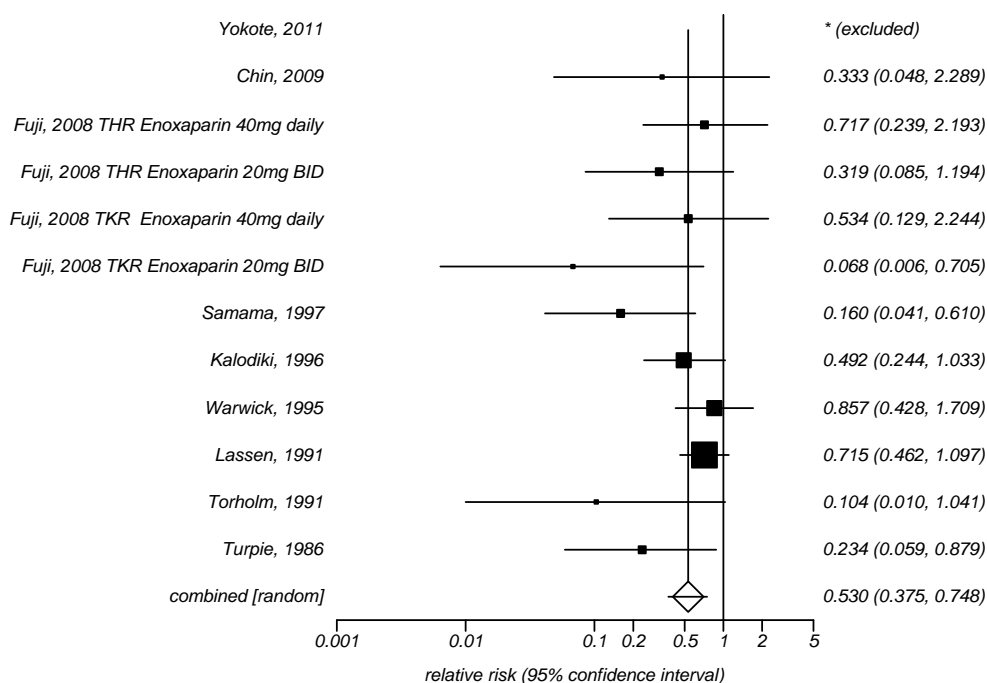


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 39. Impact of injectable low molecular weight heparins versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

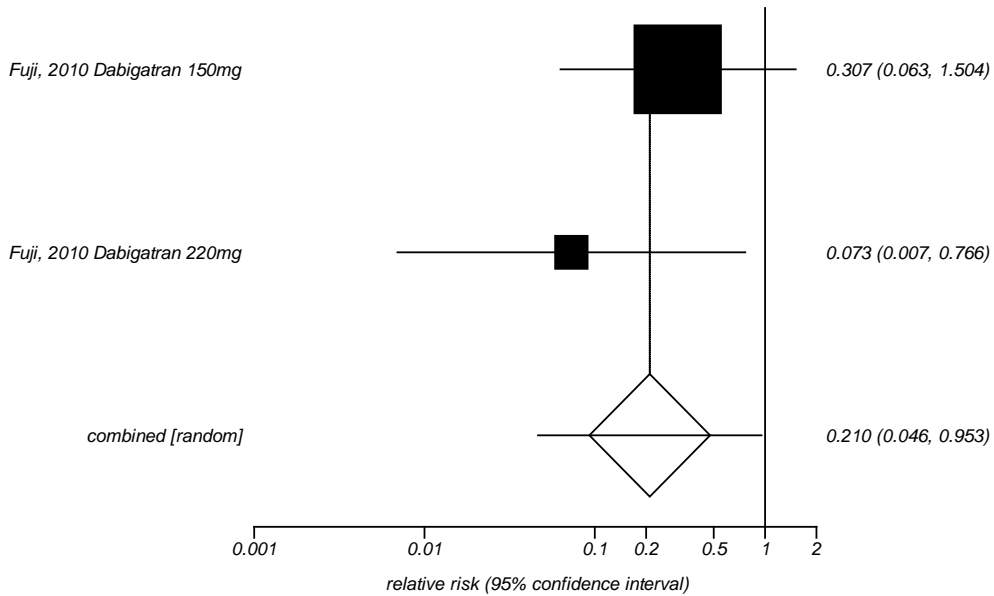


I²: 14.3 percent
Egger's p-value: 0.003

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 40. Impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

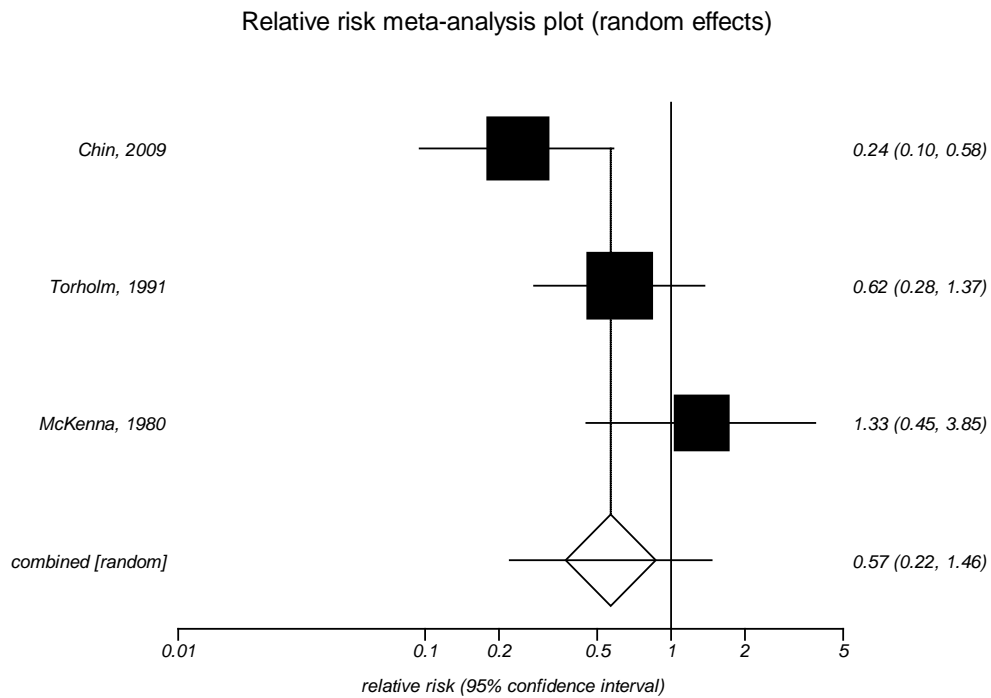


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

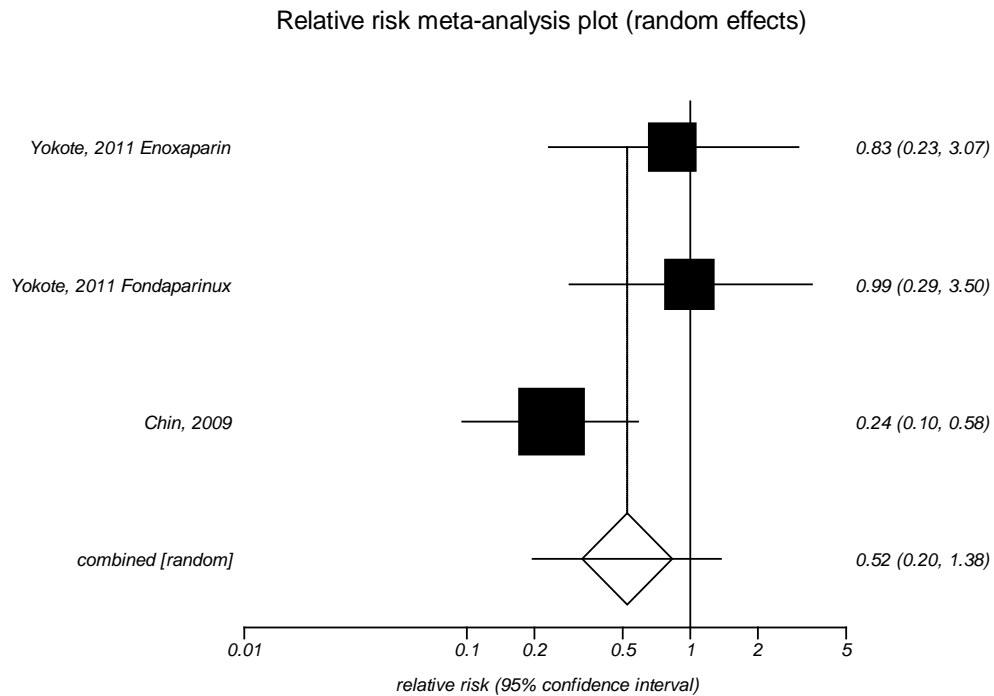
Figure 41. Impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to truly no prophylaxis trials



I^2 : 66.8 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

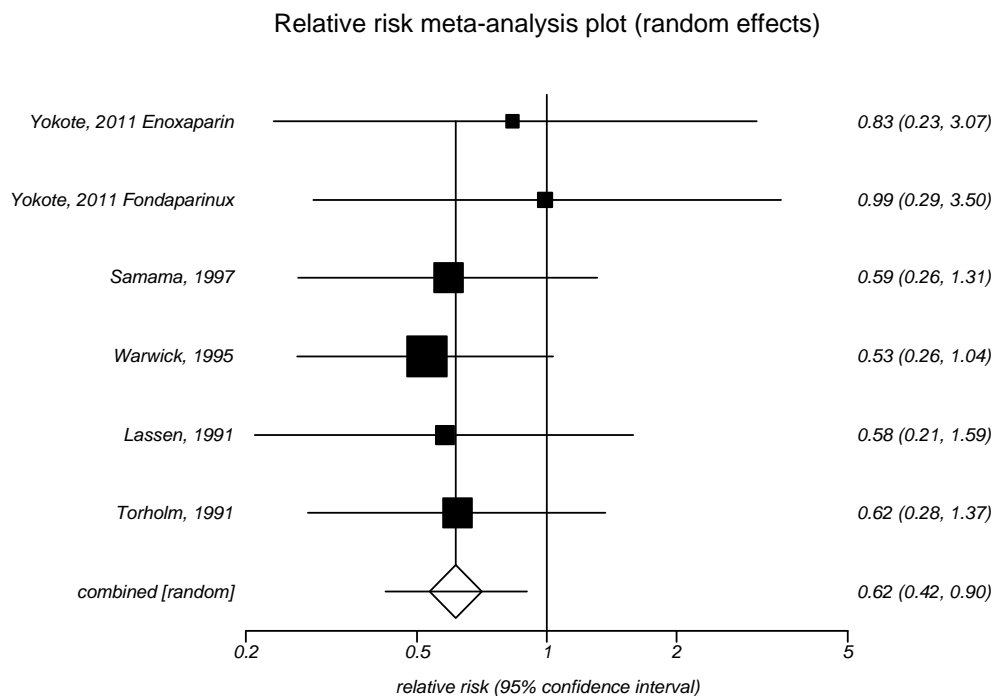
Figure 42. Impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 48.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 43. Impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement

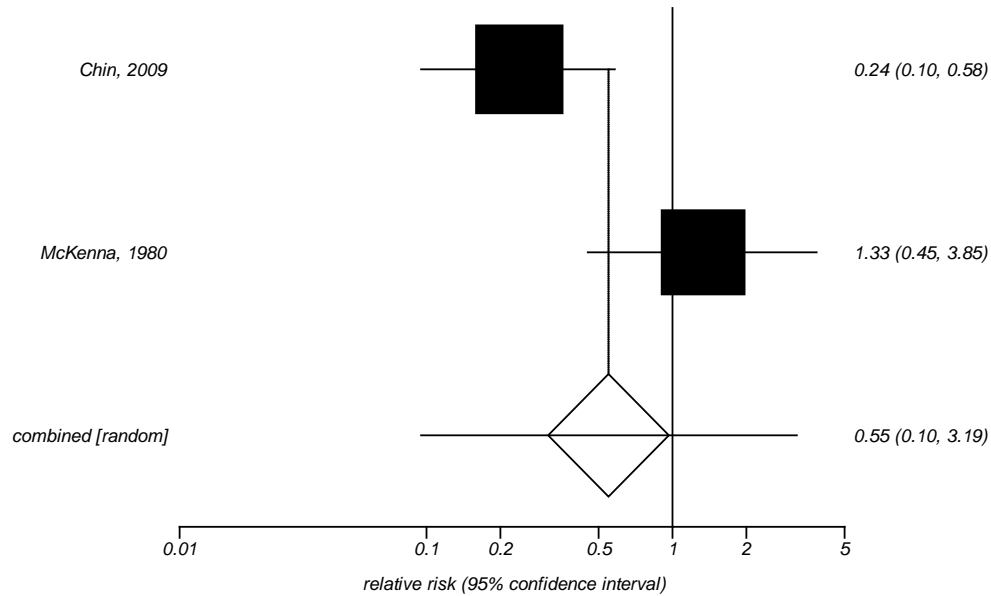


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 44. Impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to total knee replacement

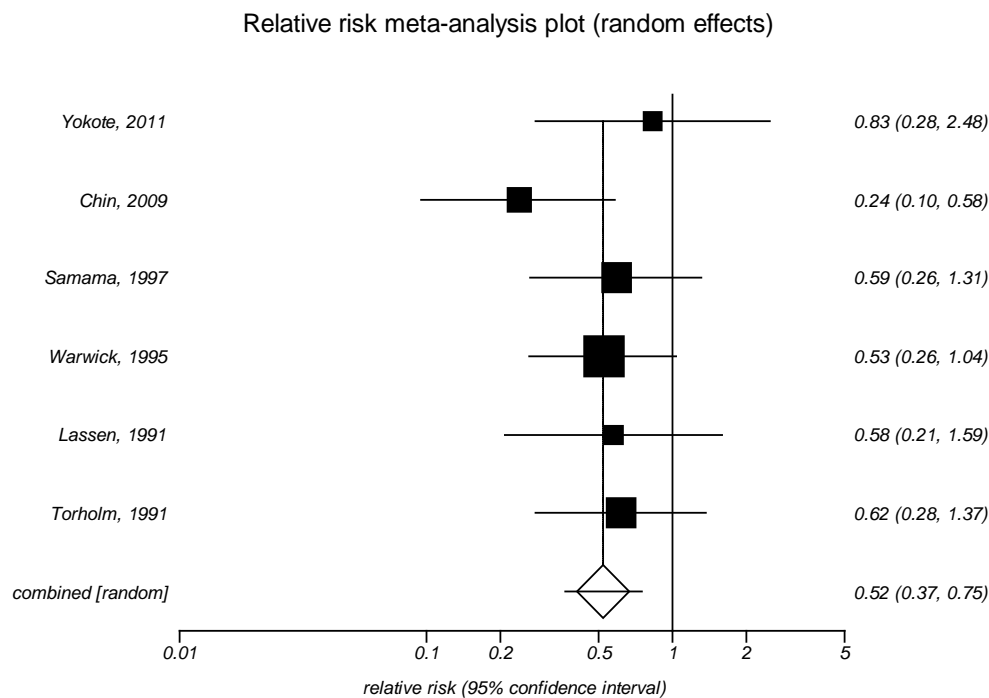
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

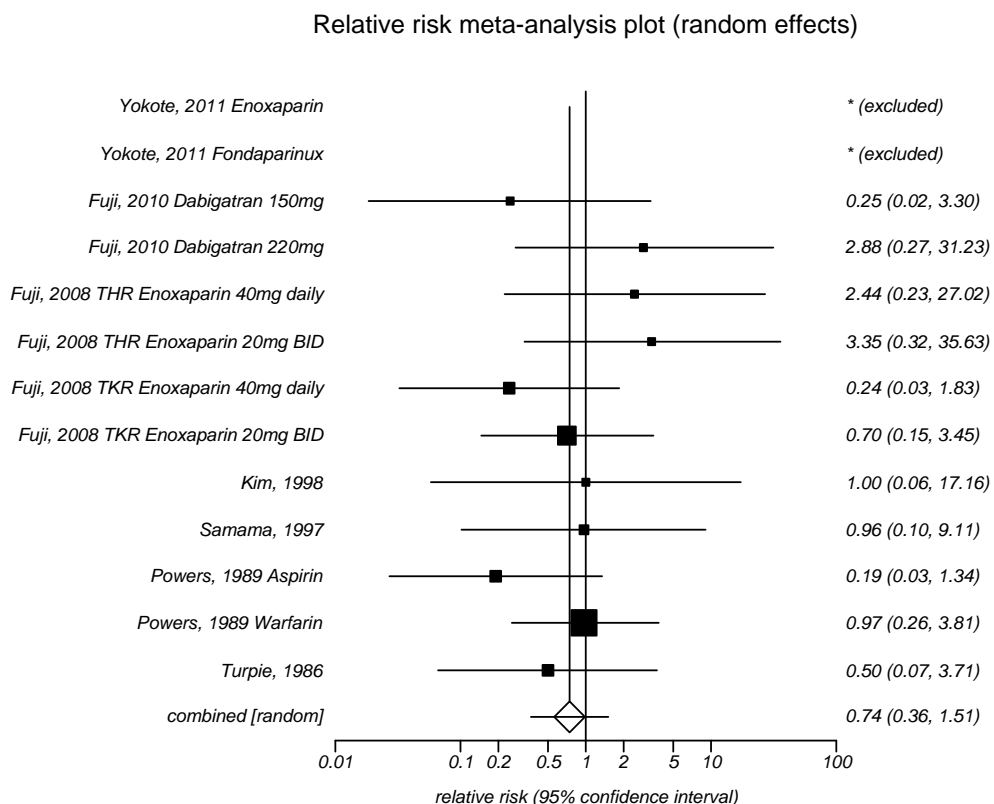
Figure 45. Impact of injectable low molecular weight heparins versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 0 percent
 Egger's p-value: 0.892

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

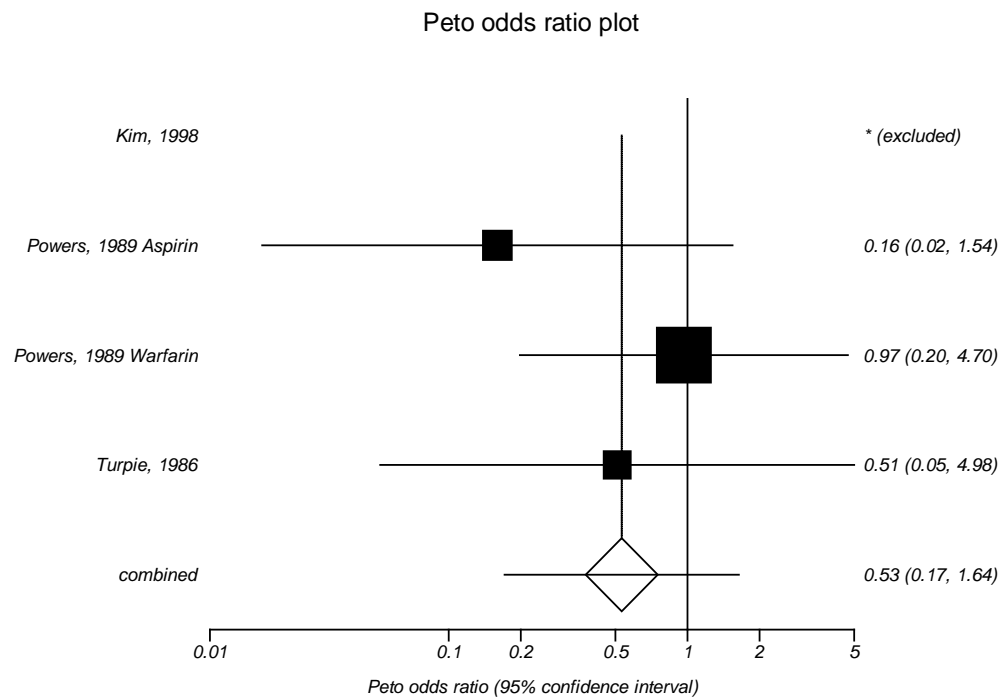
Figure 46. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.707

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 47. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery limited to truly no prophylaxis trials

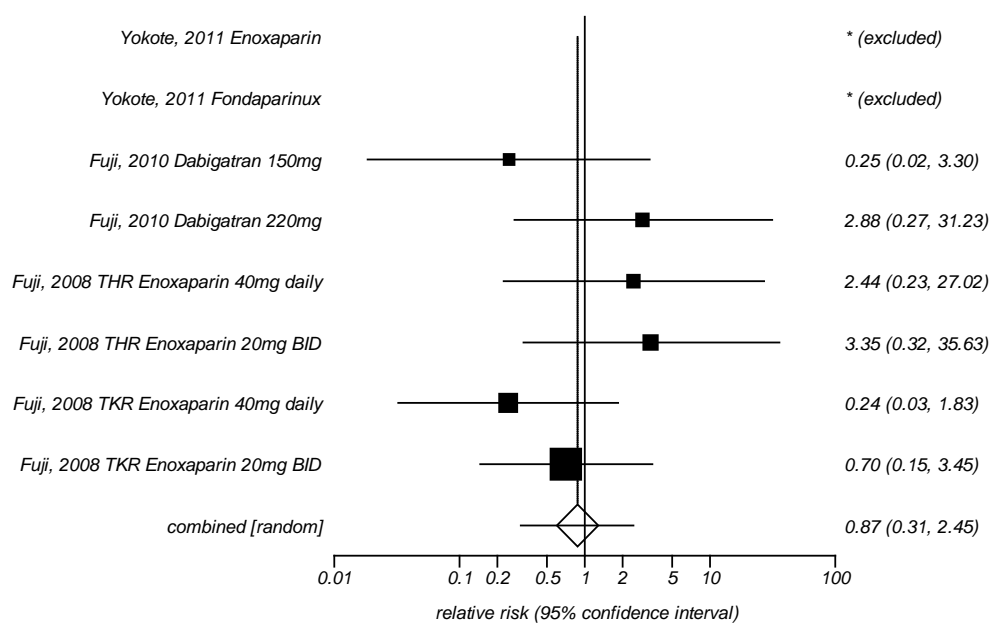


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 48. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery limited to trials published from 2001-present

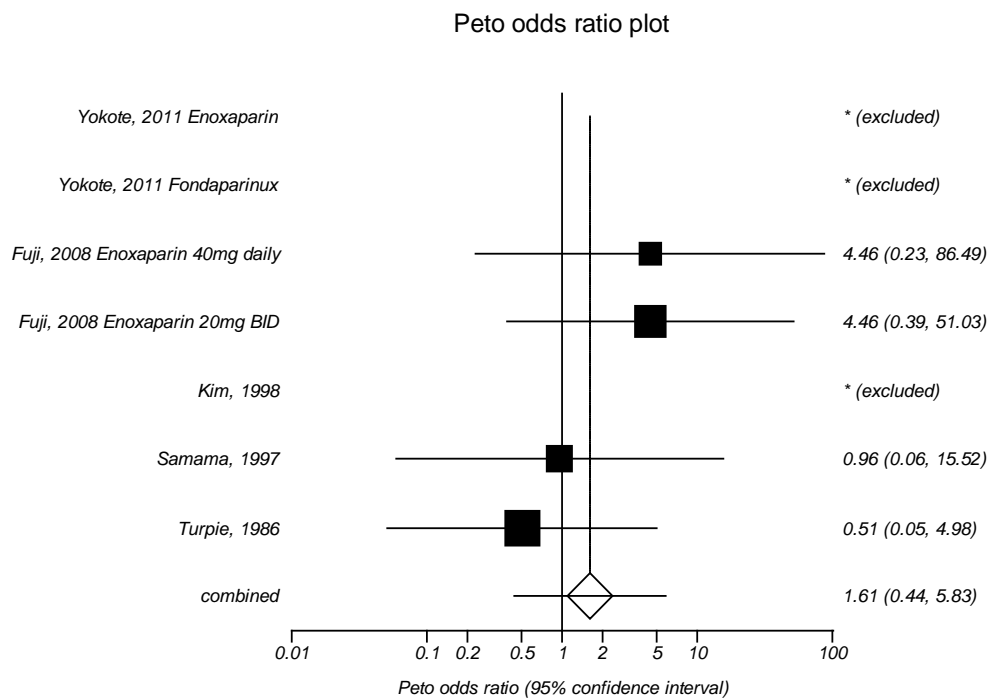
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

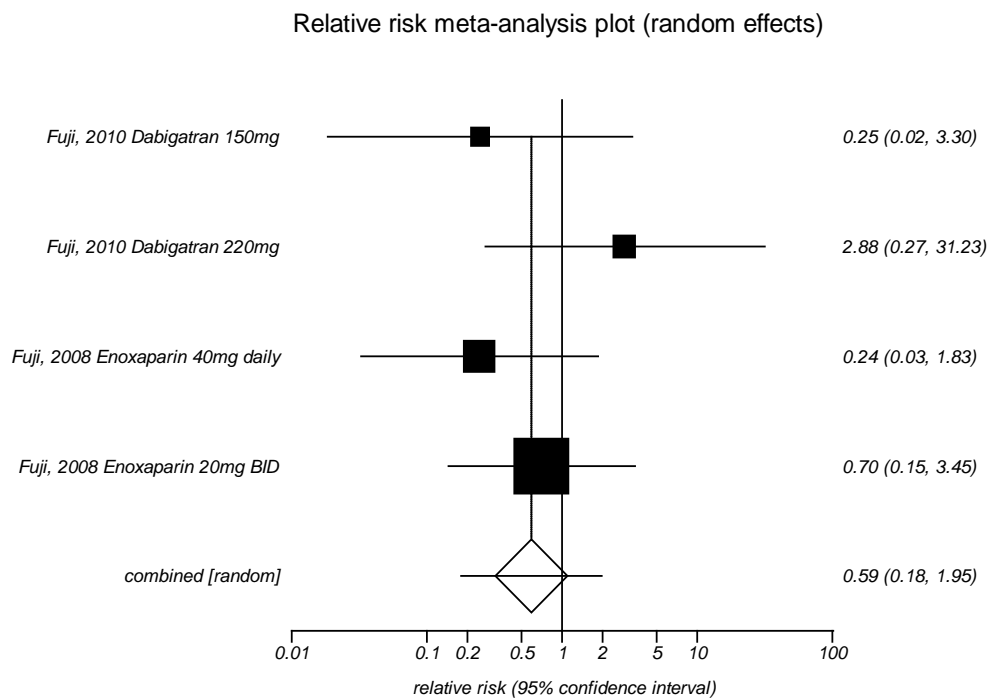
Figure 49. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery limited to total hip replacement



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

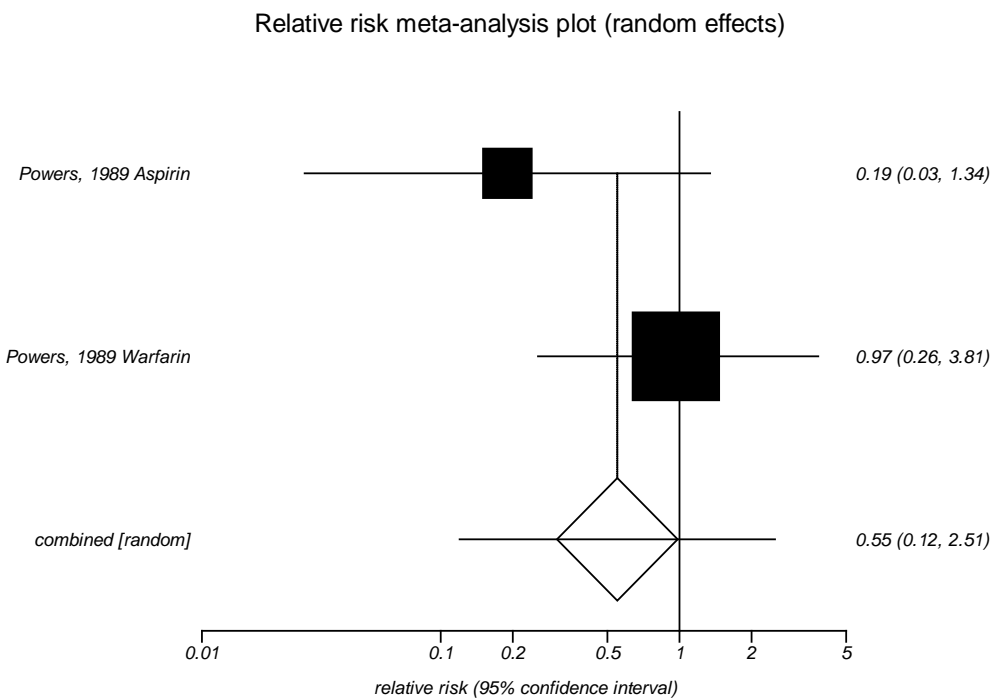
Figure 50. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who major orthopedic surgery limited to total knee replacement



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 51. Impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery limited to hip fracture surgery

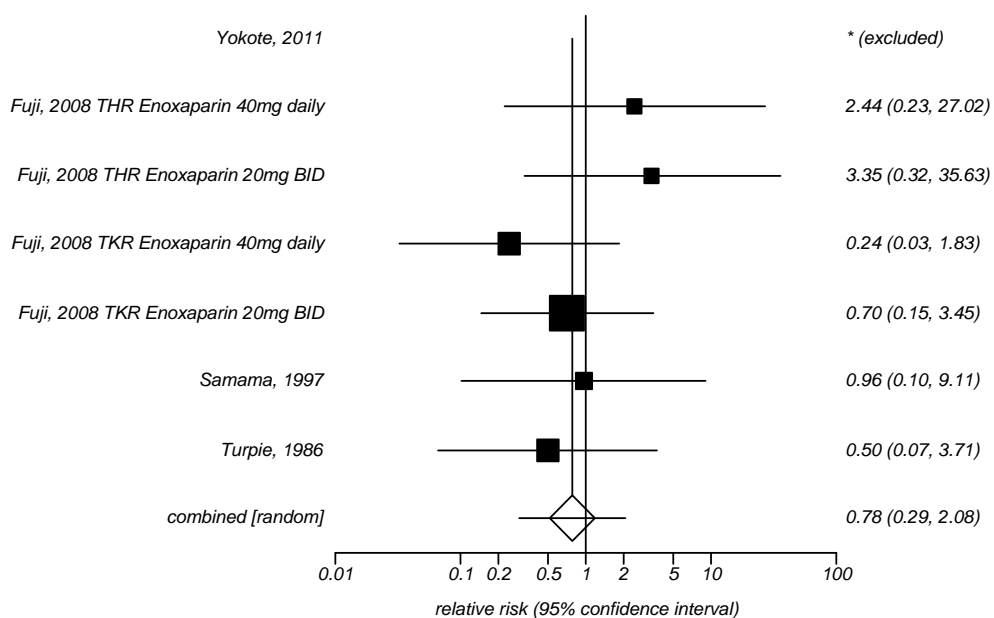


I^2 : too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 52. Impact of injectable low molecular weight heparins versus no prophylaxis on major bleeding in patients who had major orthopedic surgery

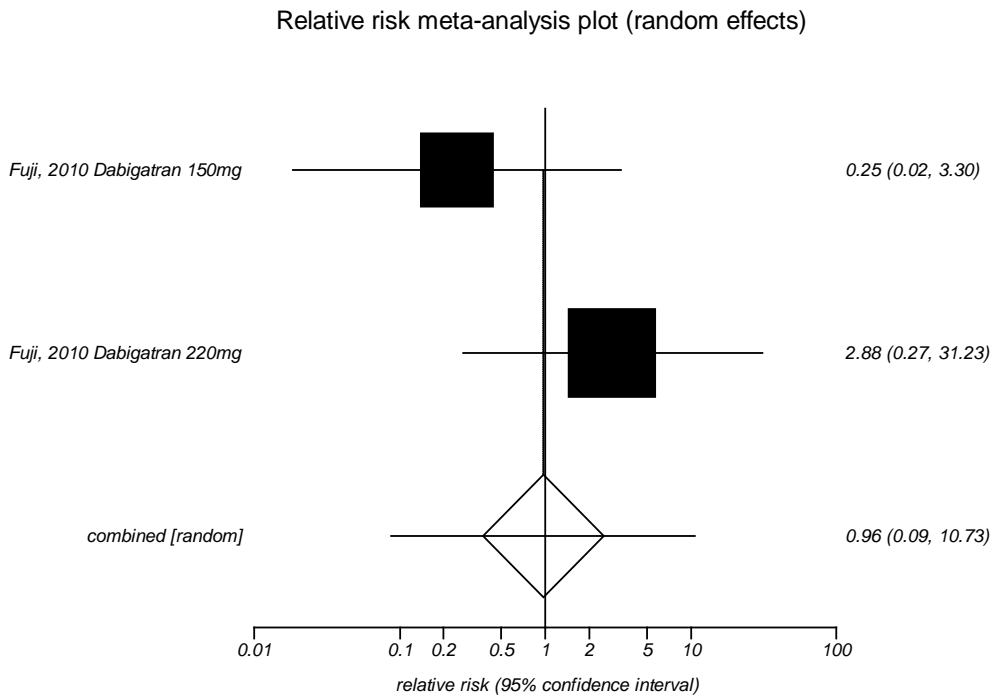
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent
 Egger's p-value: 0.275

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 53. Impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on major bleeding in patients who had major orthopedic surgery



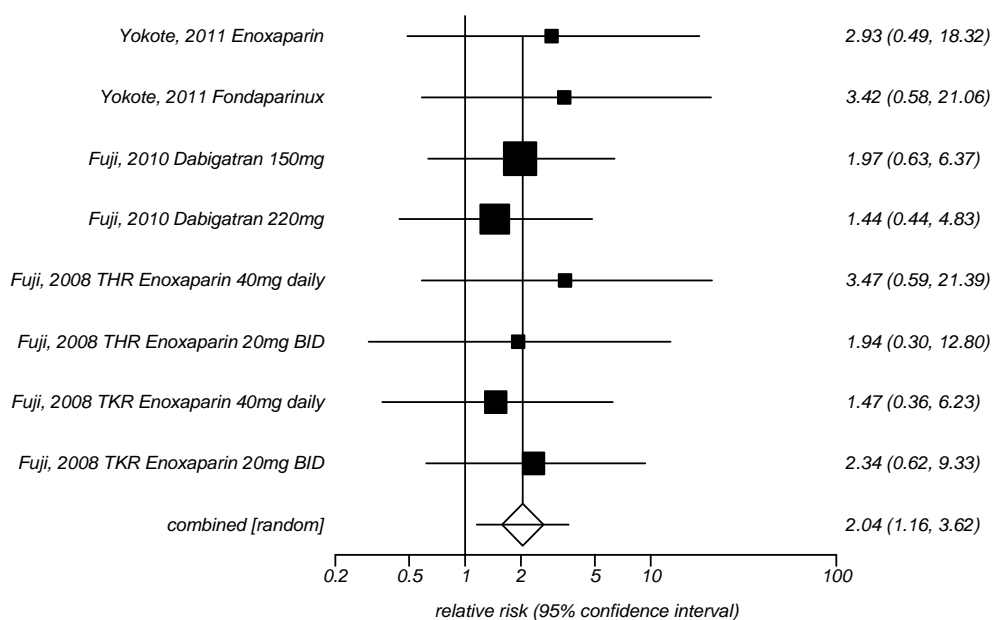
I^2 : too few strata

Egger's p-value: too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 54. Impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery limited to trials published from 2001-present

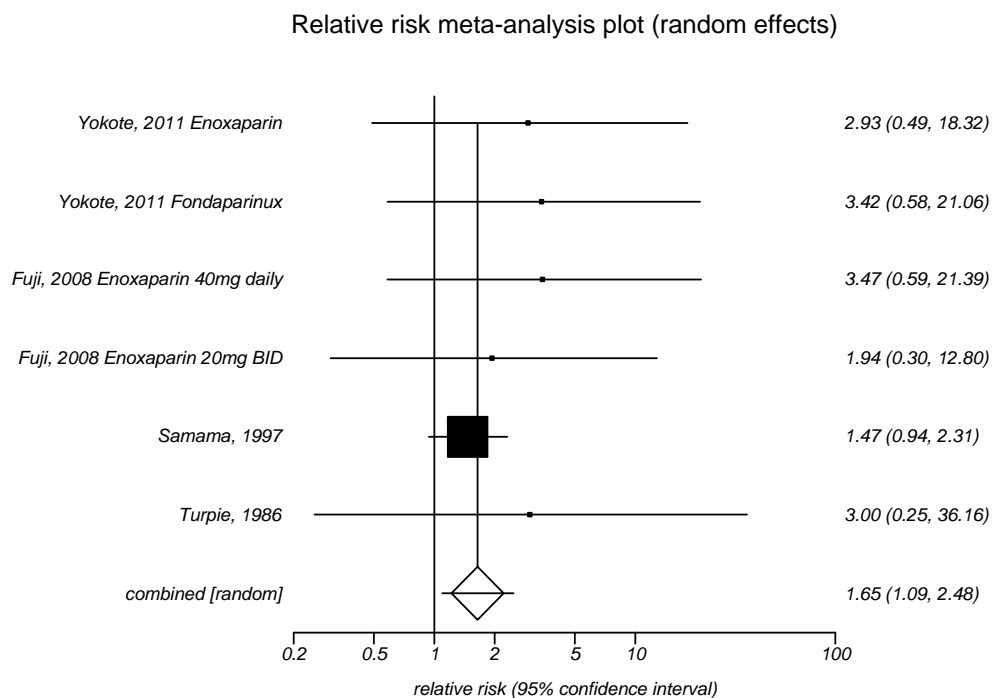
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

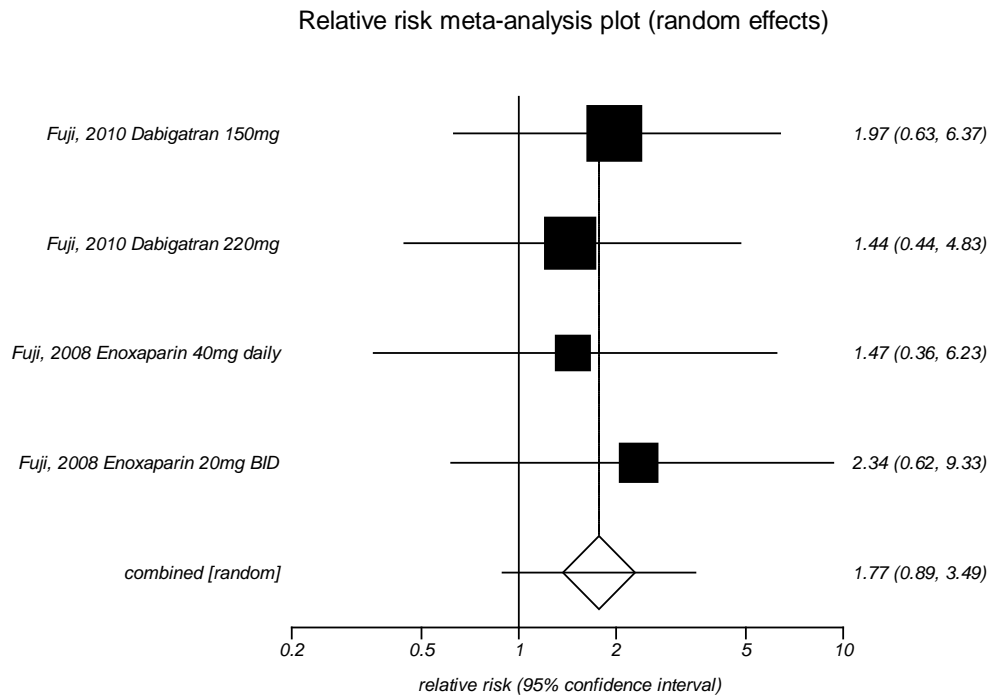
Figure 55. Impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery limited to total hip replacement



I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

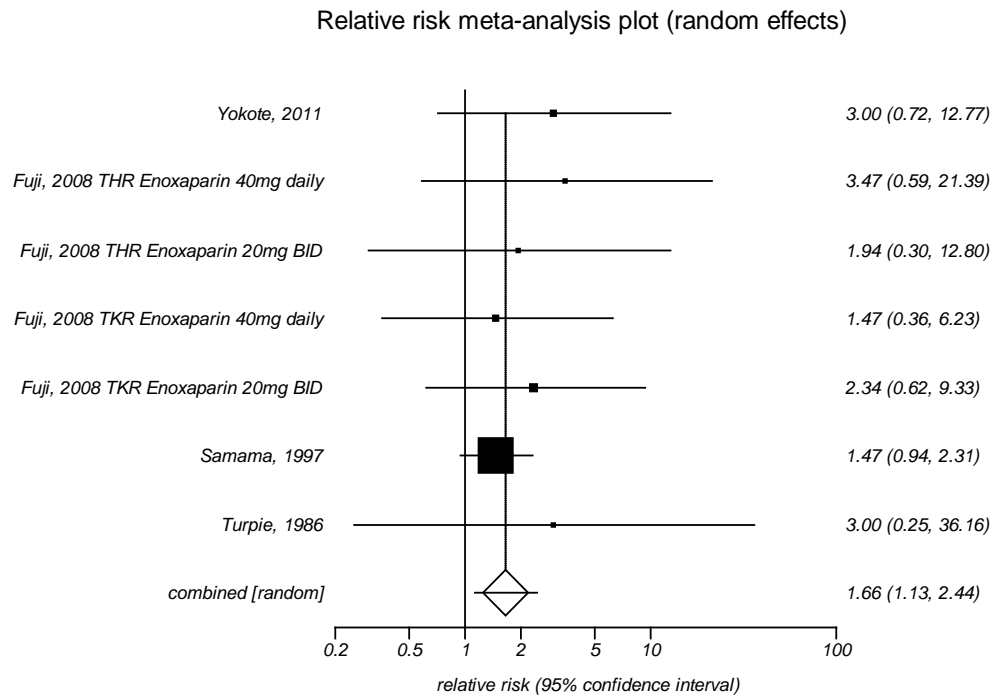
Figure 56. Impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery limited to total knee replacement



I^2 : 0 percent
 Egger's p-value: 0.974

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

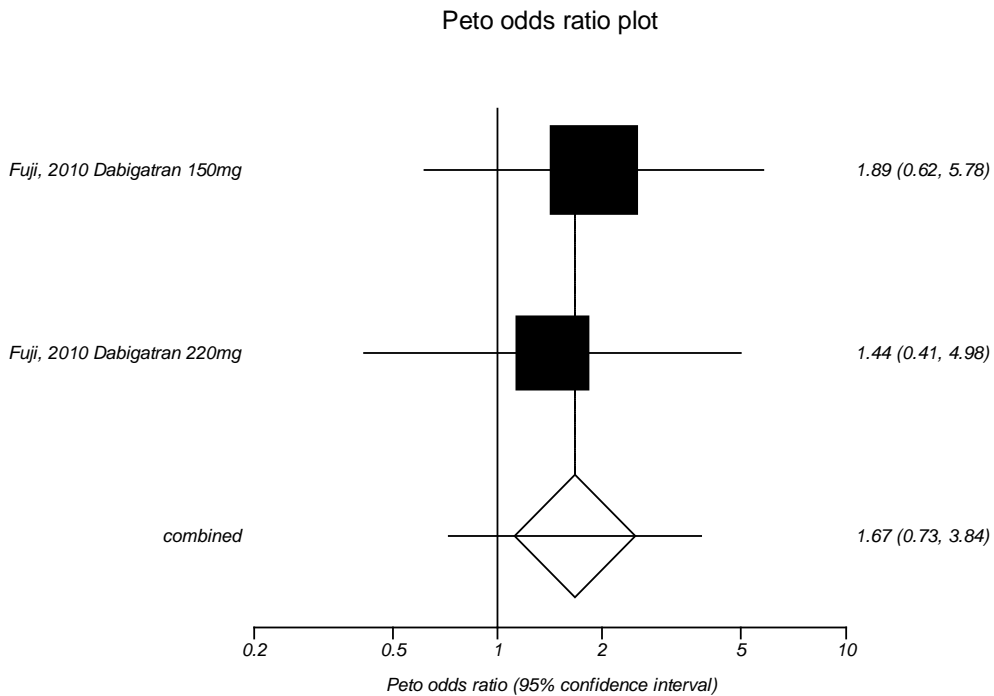
Figure 57. Impact of injectable low molecular weight heparins versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 58. Impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery

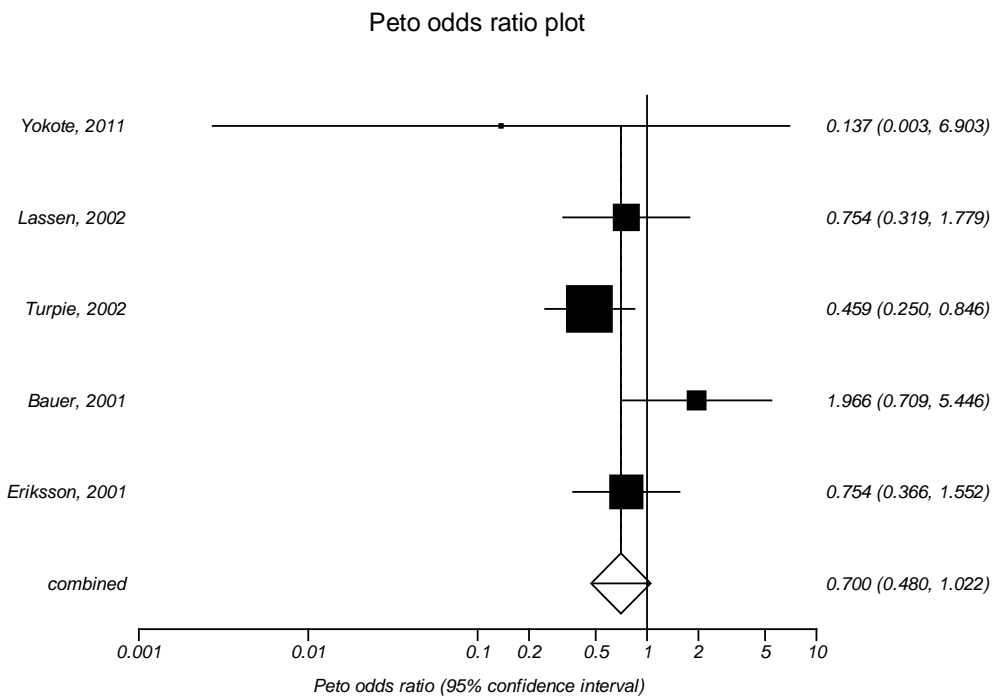


I^2 : too few strata

Egger's p-value: too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

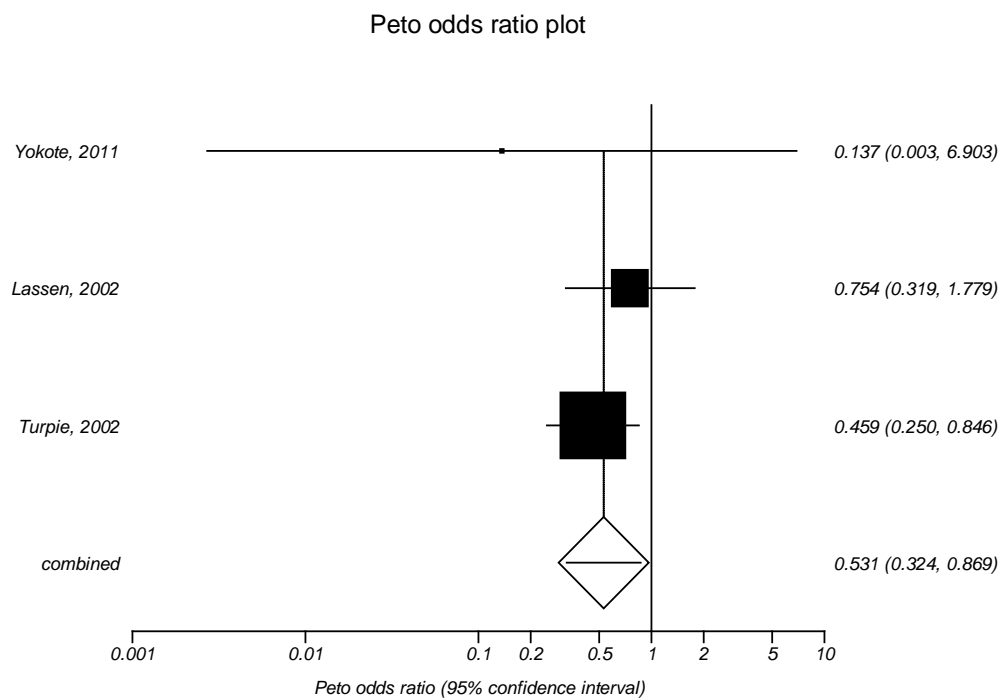
Figure 59. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on symptomatic objectively confirmed venous thromboembolism in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001 to the present)



I^2 : 38.5 percent
 Egger's p-value: 0.895

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

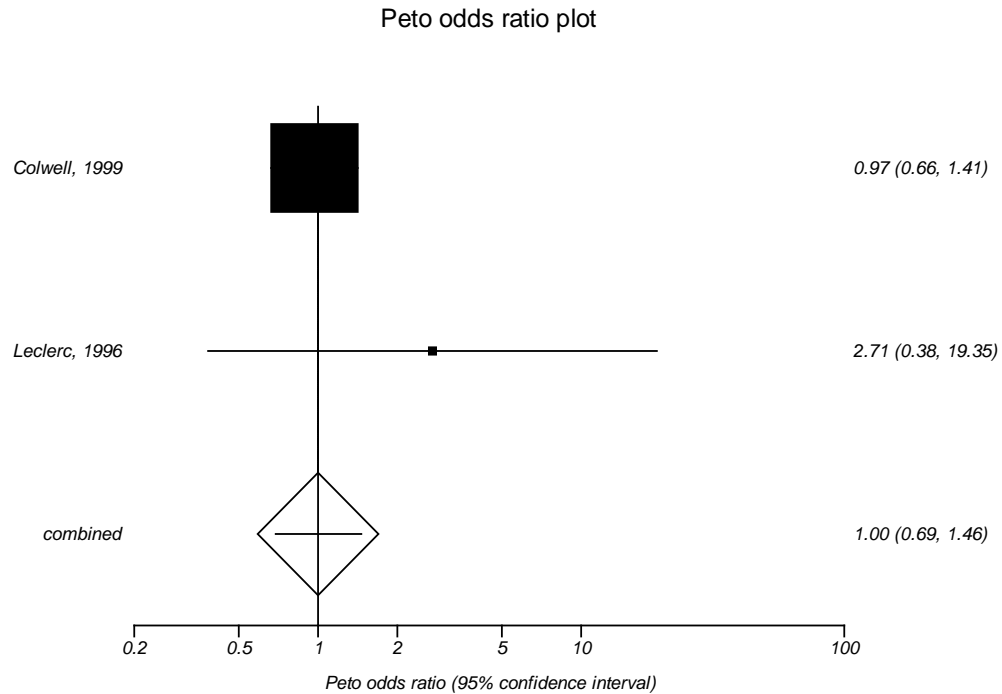
Figure 60. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on symptomatic objectively confirmed venous thromboembolism in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 61. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients undergoing major orthopedic surgery

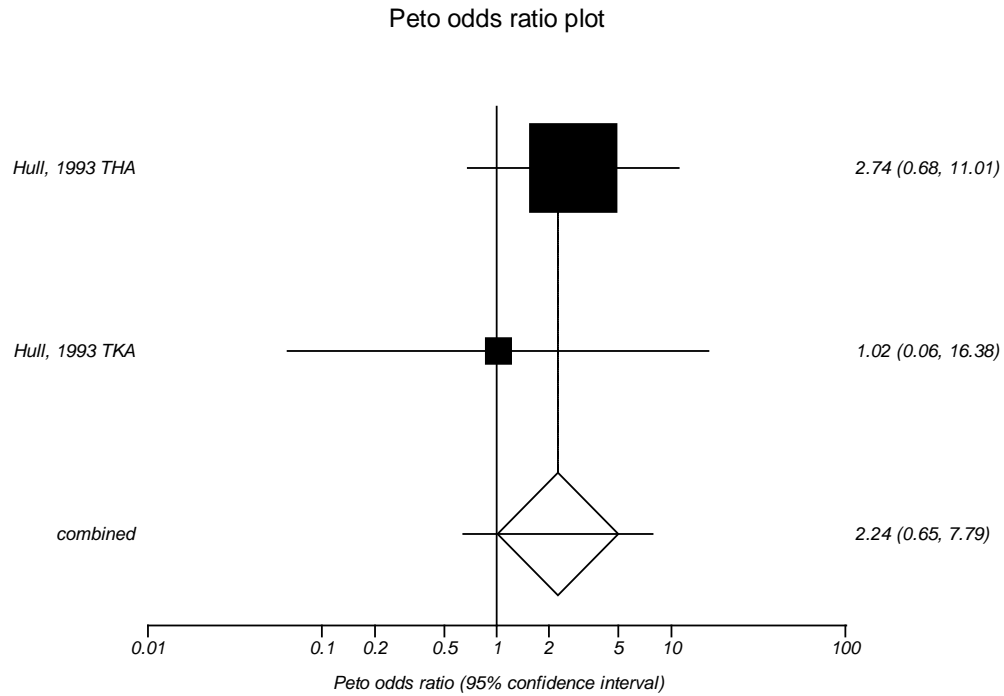


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 62. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on symptomatic objectively confirmed venous thromboembolism during the postdischarge period in patients who had major orthopedic surgery

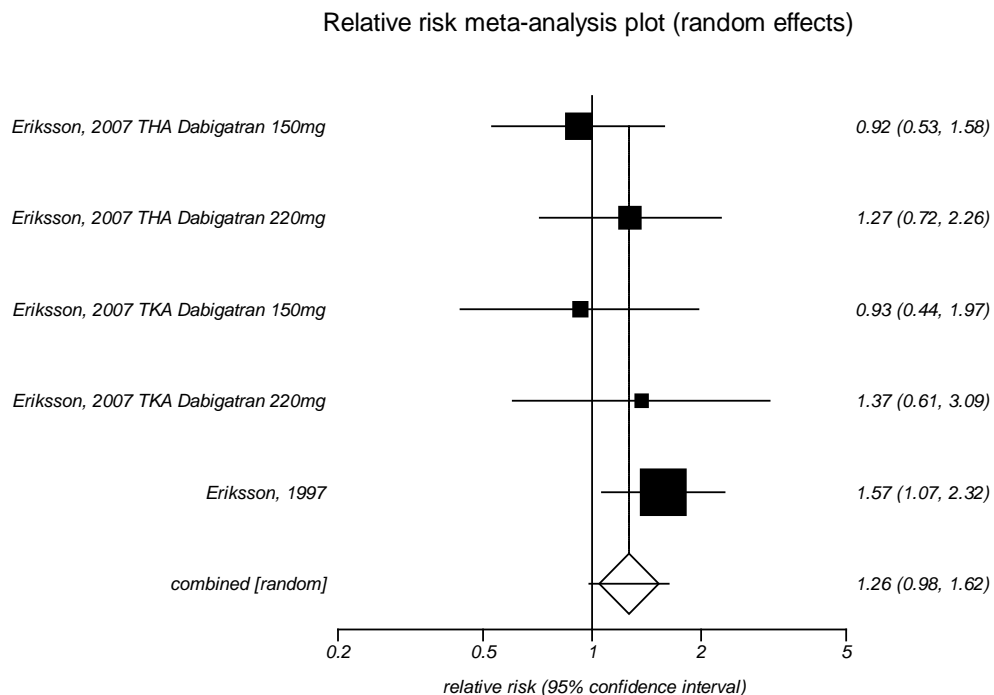


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

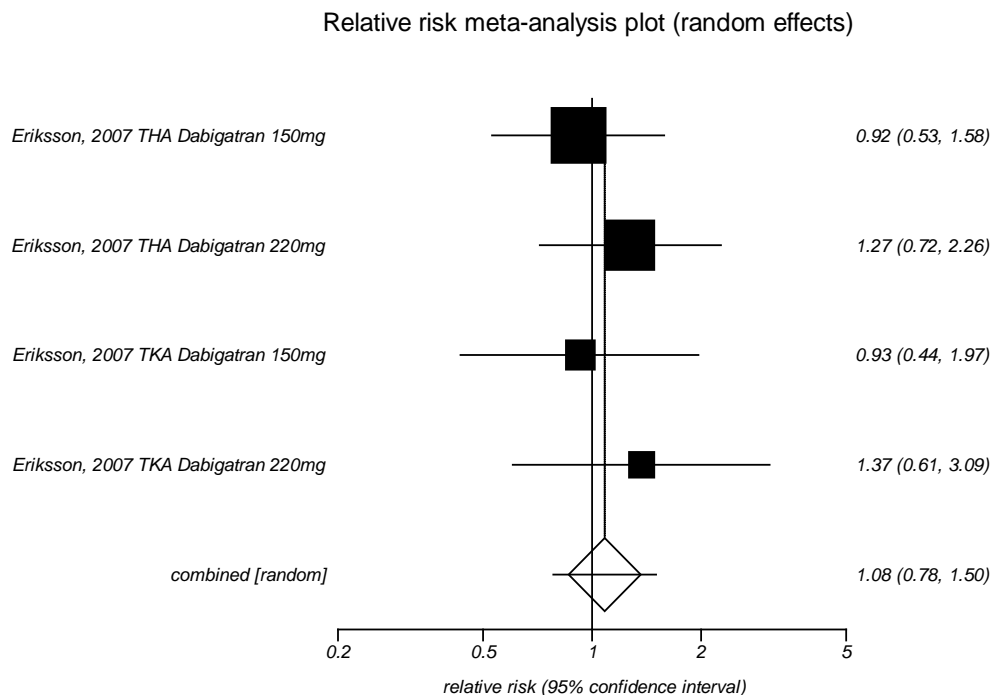
Figure 63. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on major venous thromboembolism in patients undergoing major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.326

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

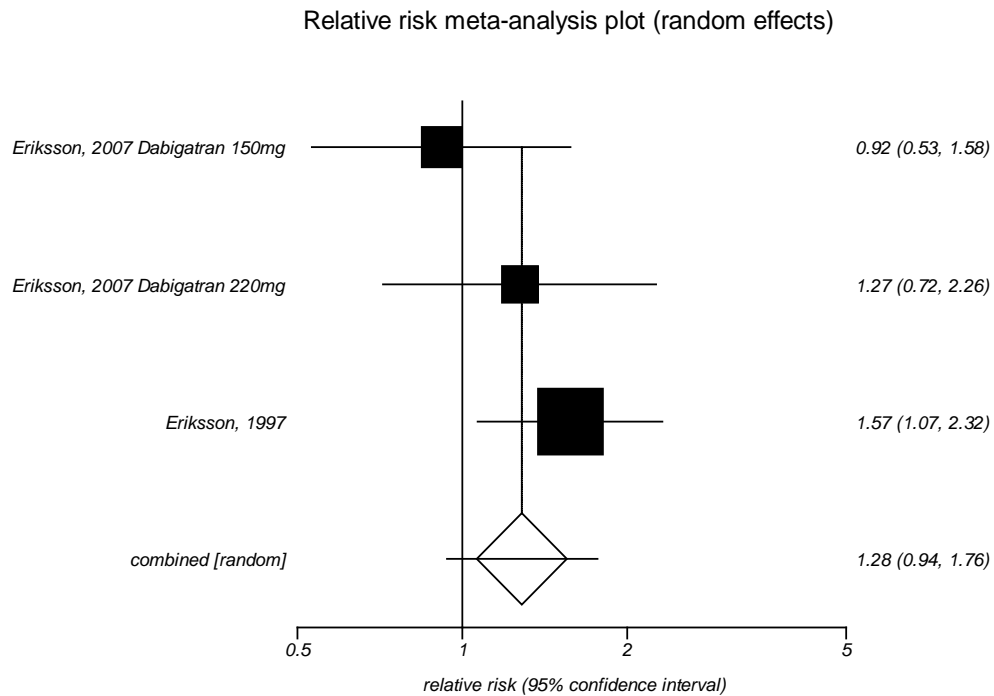
Figure 64. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on major venous thromboembolism in patients undergoing major orthopedic surgery limited to trials published from 2001 to the present



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 65. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on major venous thromboembolism in patients undergoing major orthopedic surgery limited to total hip replacement

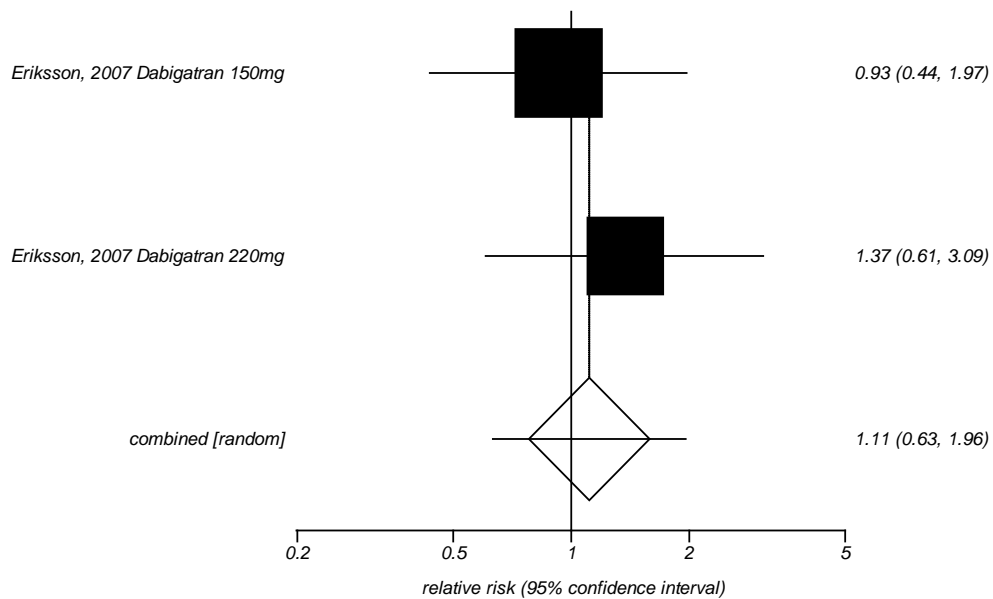


I^2 : 18.6 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 66. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on major venous thromboembolism in patients undergoing major orthopedic surgery limited to total knee replacement

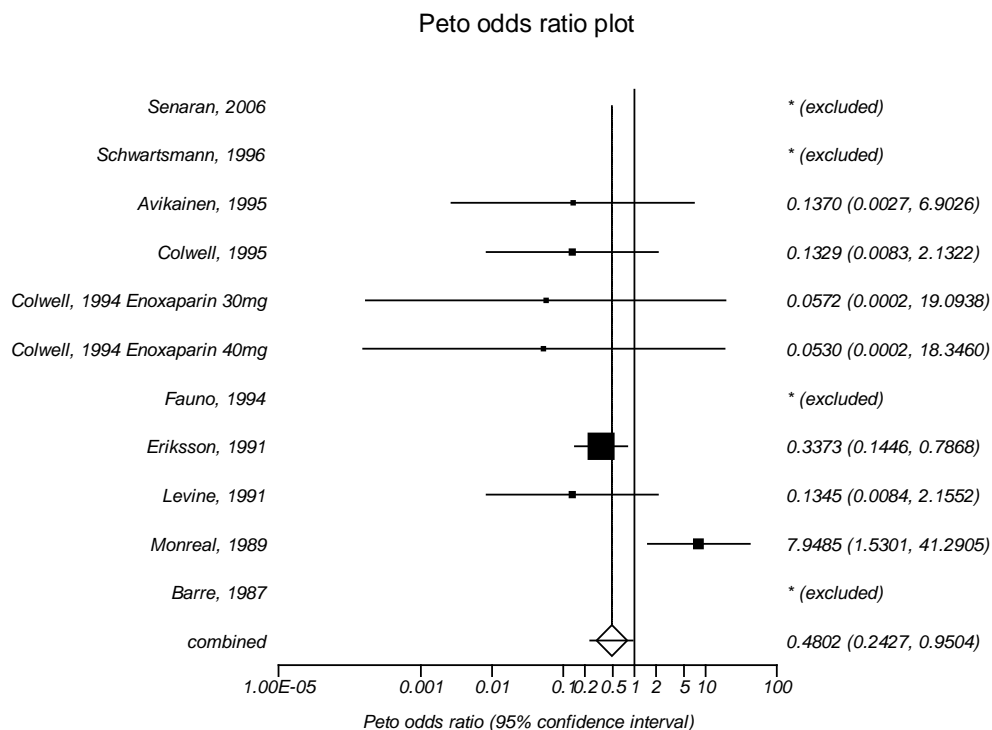
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 67. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on pulmonary embolism in patients undergoing major orthopedic surgery



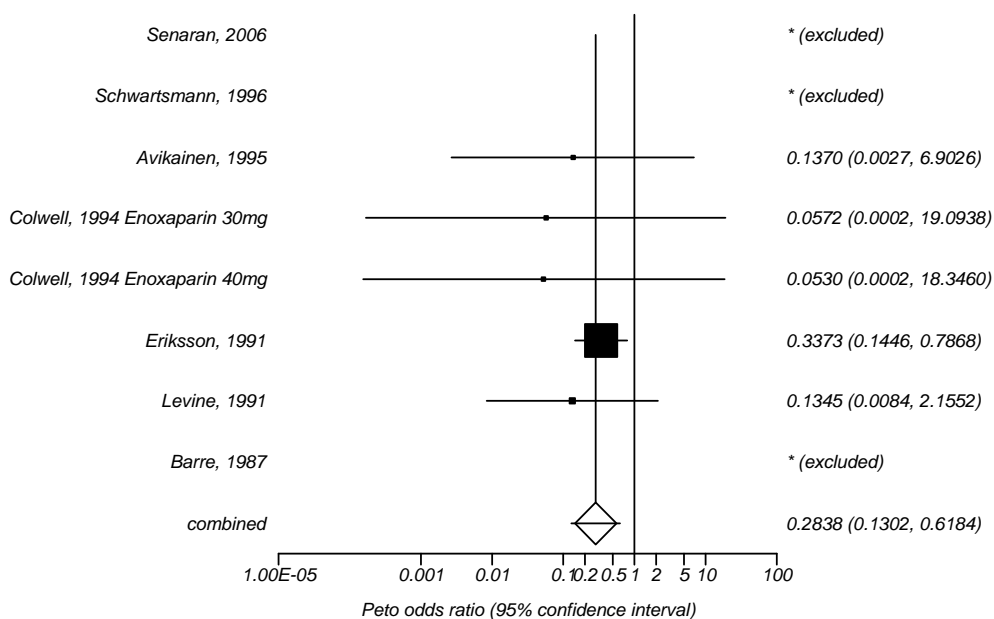
I^2 : 59.7

Egger's p-value: 0.629

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 68. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement

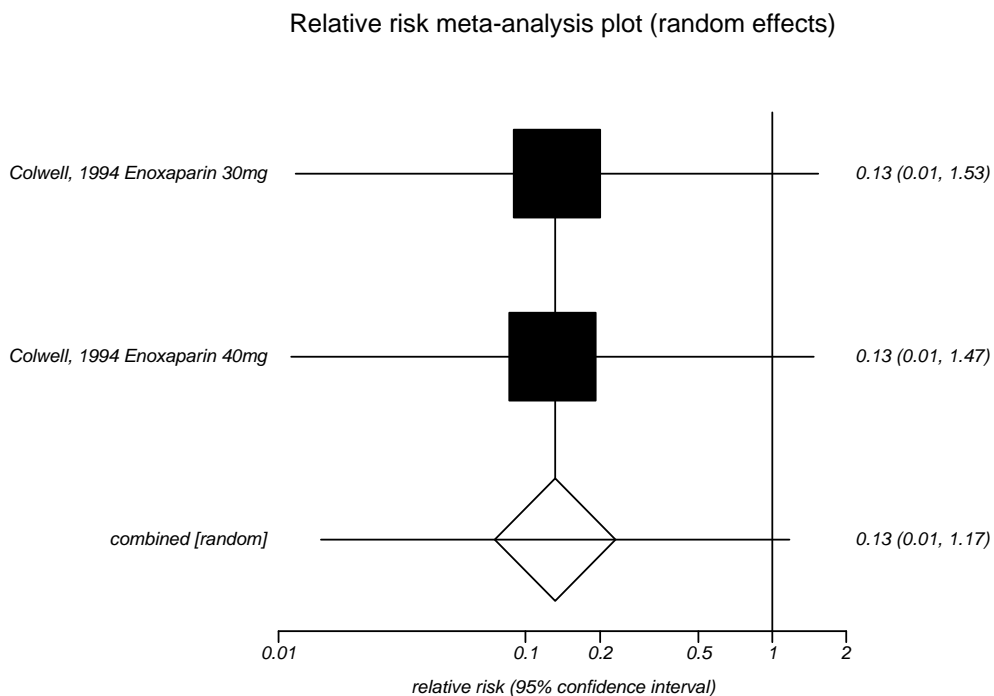
Peto odds ratio plot



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 69. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery (same as analysis of nonfatal pulmonary embolism during the post discharge period)



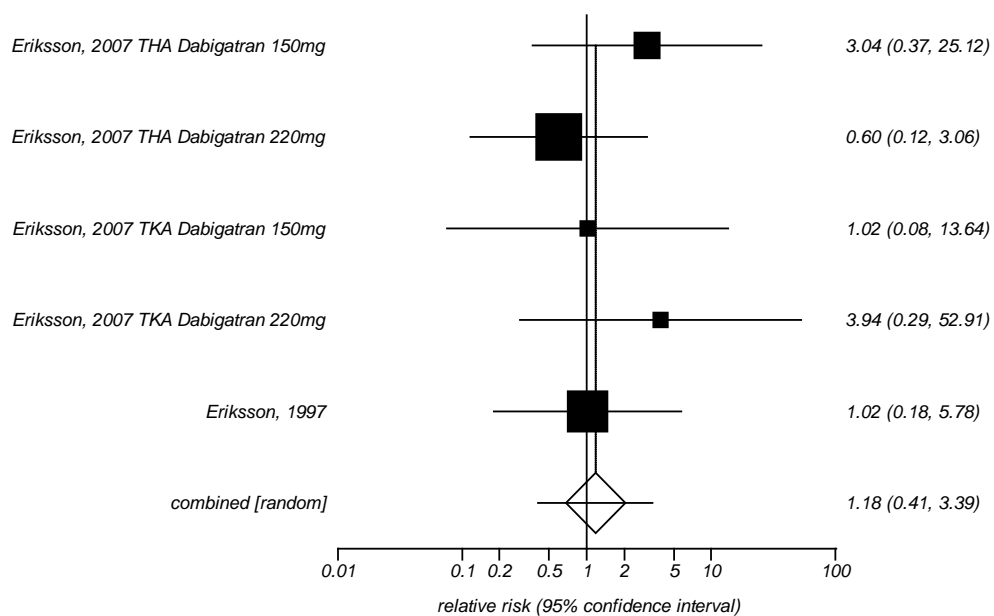
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 70. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on pulmonary embolism in patients undergoing major orthopedic surgery

Relative risk meta-analysis plot (random effects)

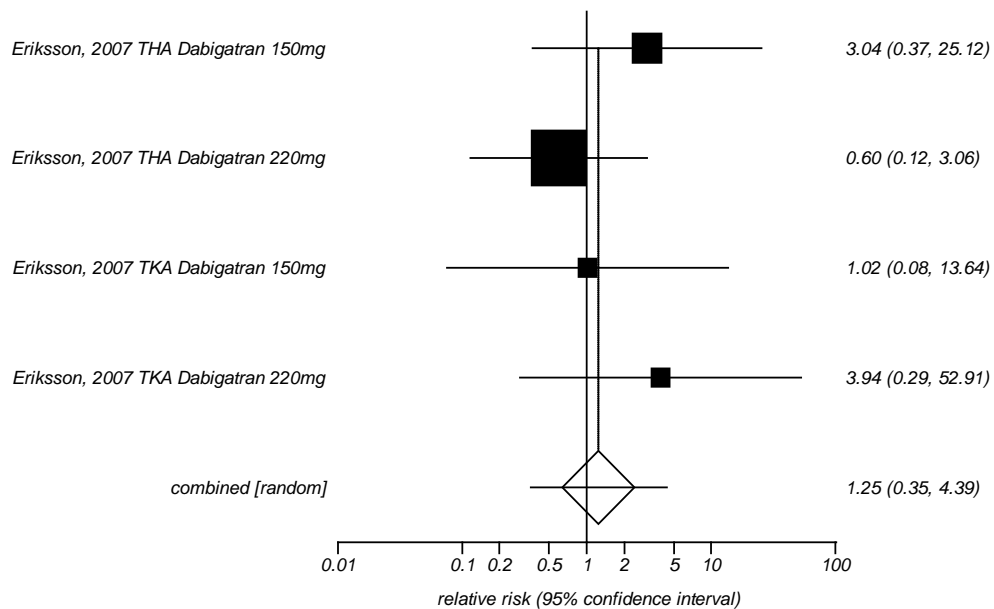


I^2 : 0 percent
Egger's p-value: 0.208

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 71. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on pulmonary embolism in patients undergoing major orthopedic surgery limited to trials published from 2001 to the present

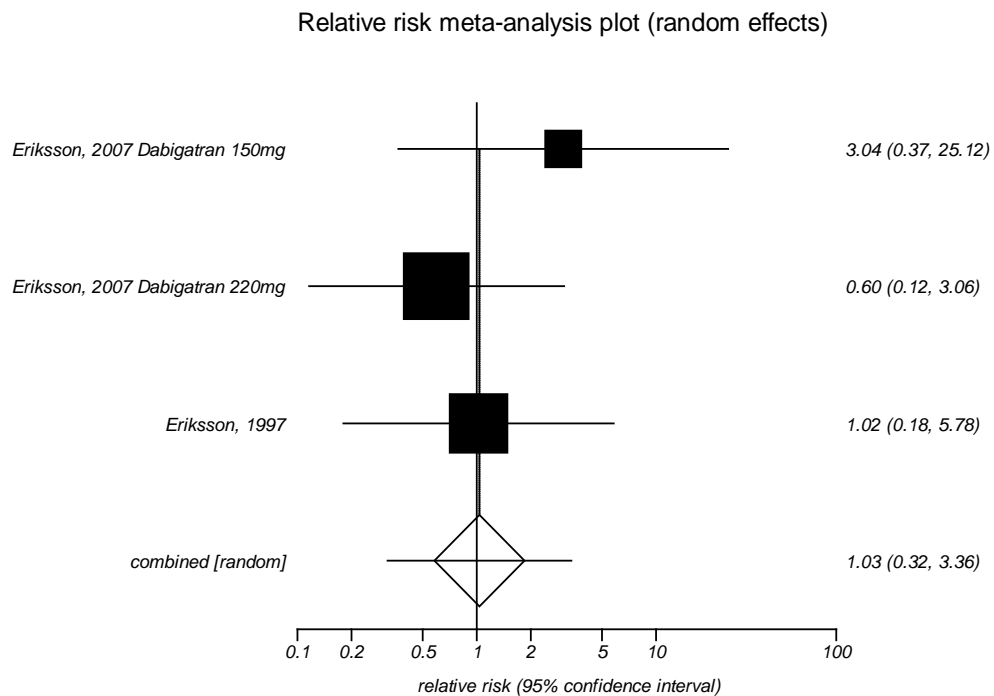
Relative risk meta-analysis plot (random effects)



$I^2: 0$ percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

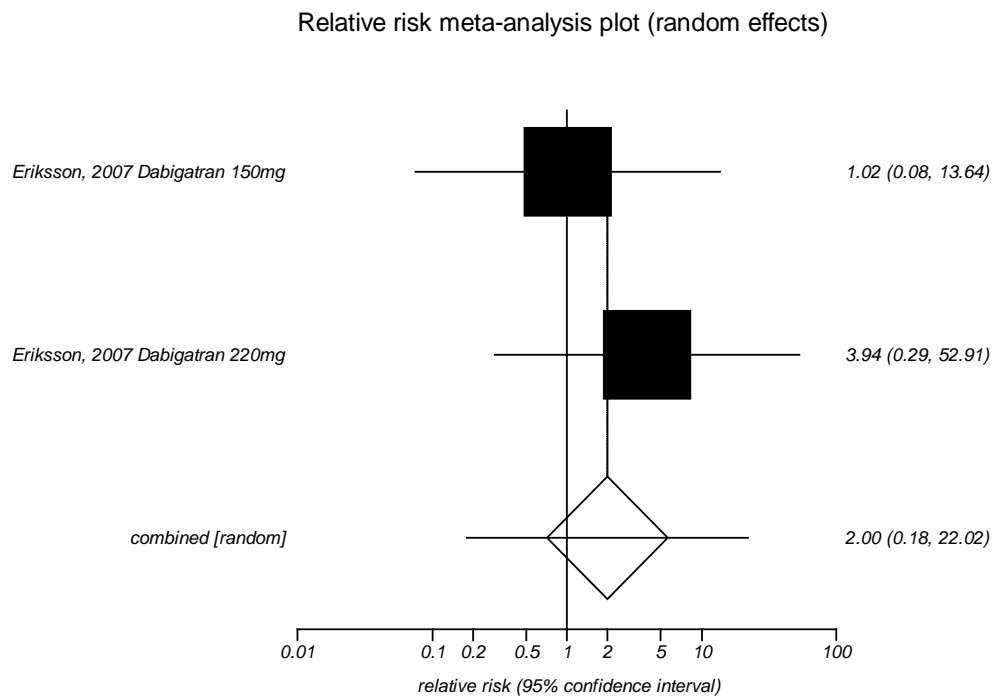
Figure 72. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

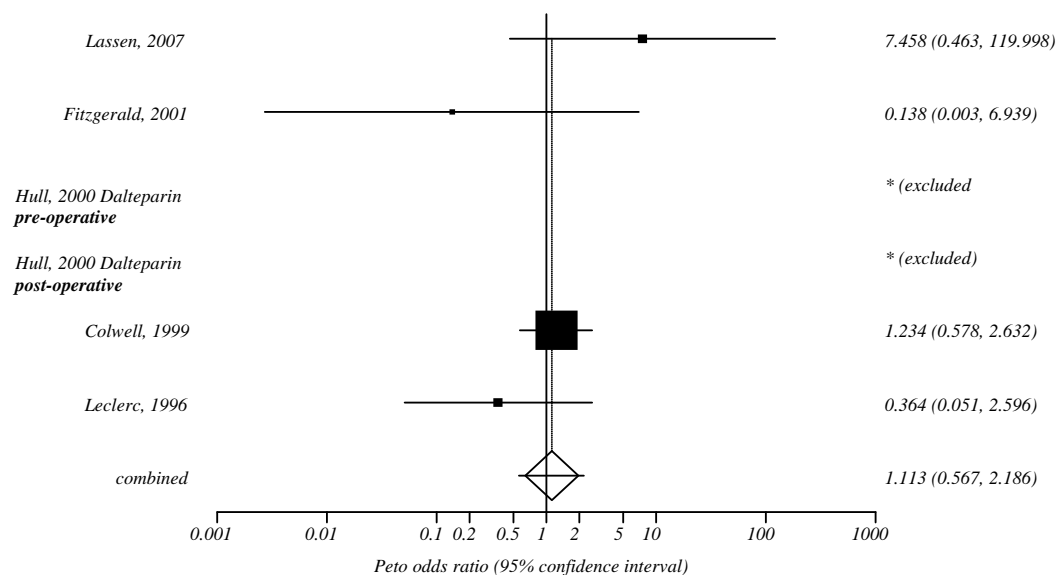
Figure 73. Impact of injectable low molecular weight heparin versus oral or injectable direct thrombin inhibitors on pulmonary embolism in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

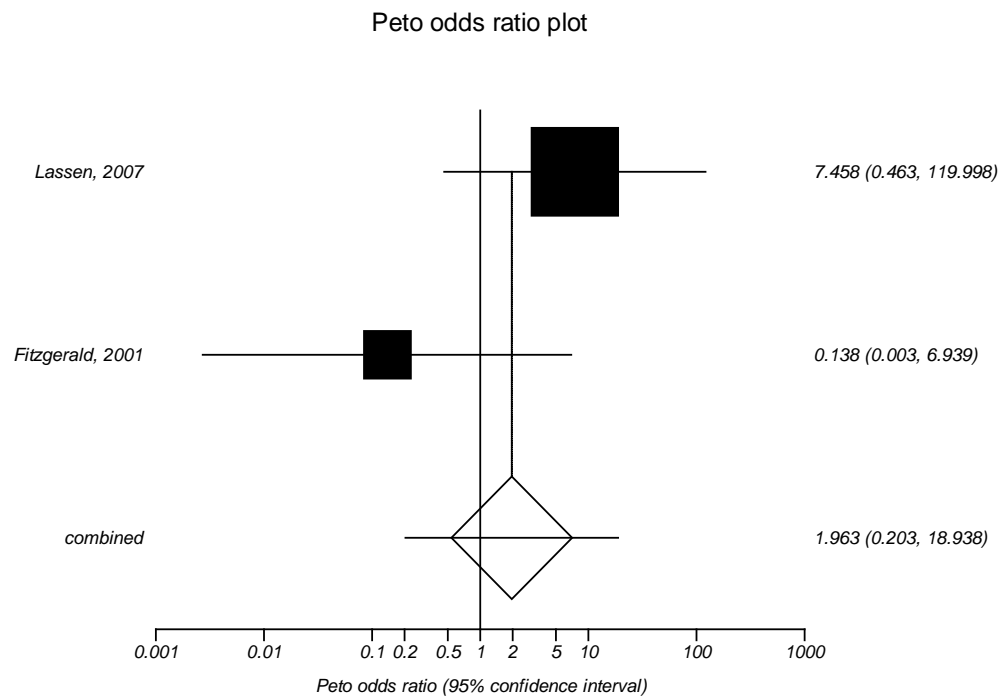
Figure 74. Impact of injectable low molecular weight heparin versus oral vitamin k antagonists on pulmonary embolism in patients undergoing major orthopedic surgery



I^2 : 28.7 percent
Egger's p-value: 0.762

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

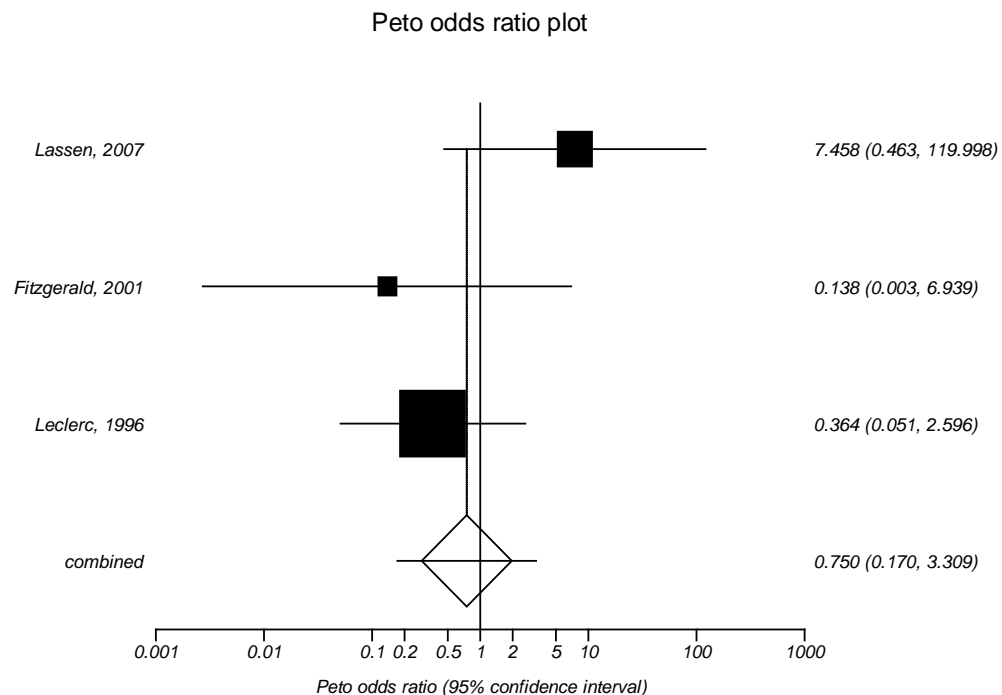
Figure 75. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on pulmonary embolism in patients undergoing major orthopedic surgery limited to trials published from 2001 to the present



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

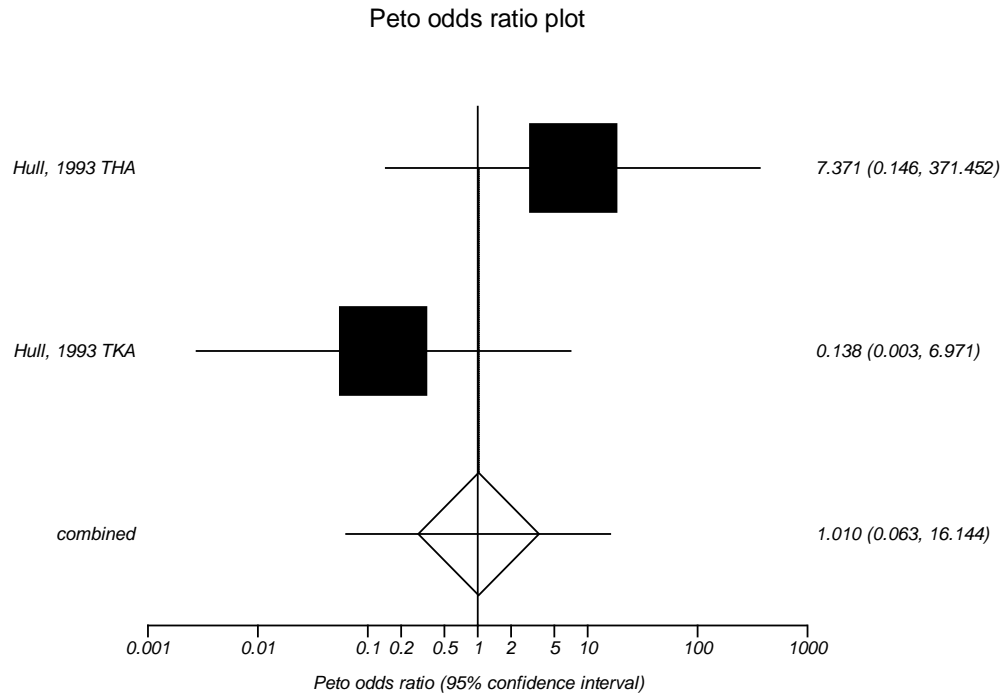
Figure 76. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on pulmonary embolism in patients undergoing major orthopedic surgery limited total knee replacement surgery



I^2 : 48.2 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 77. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery

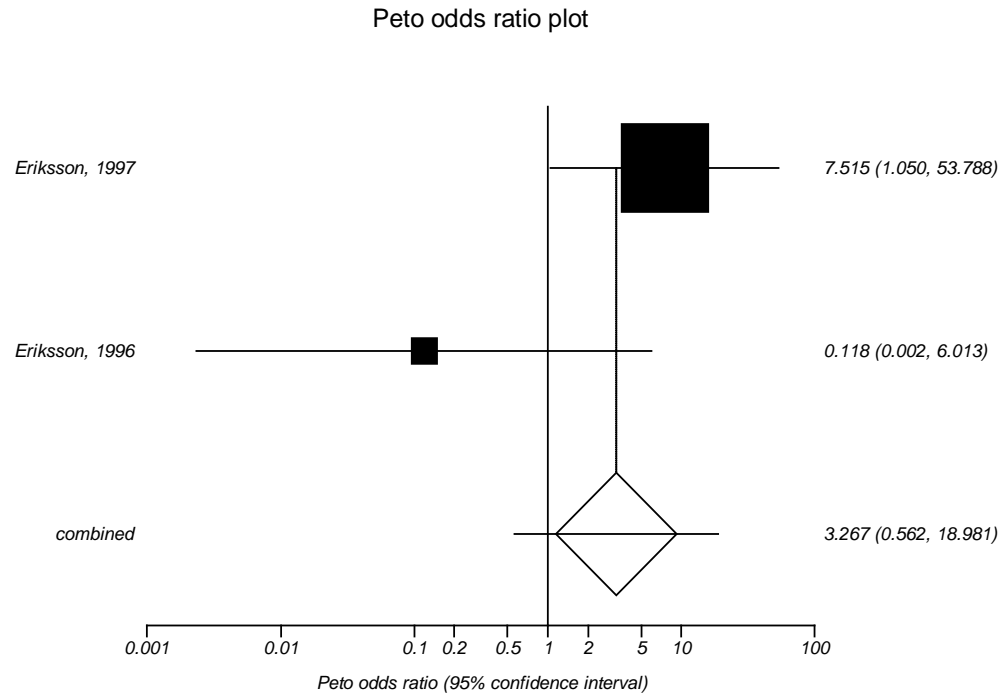


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 78. Impact of injectable unfractionated heparin versus oral or injectable direct thrombin inhibitors on pulmonary embolism in patients undergoing major orthopedic surgery (same as limited to total hip replacement surgery)

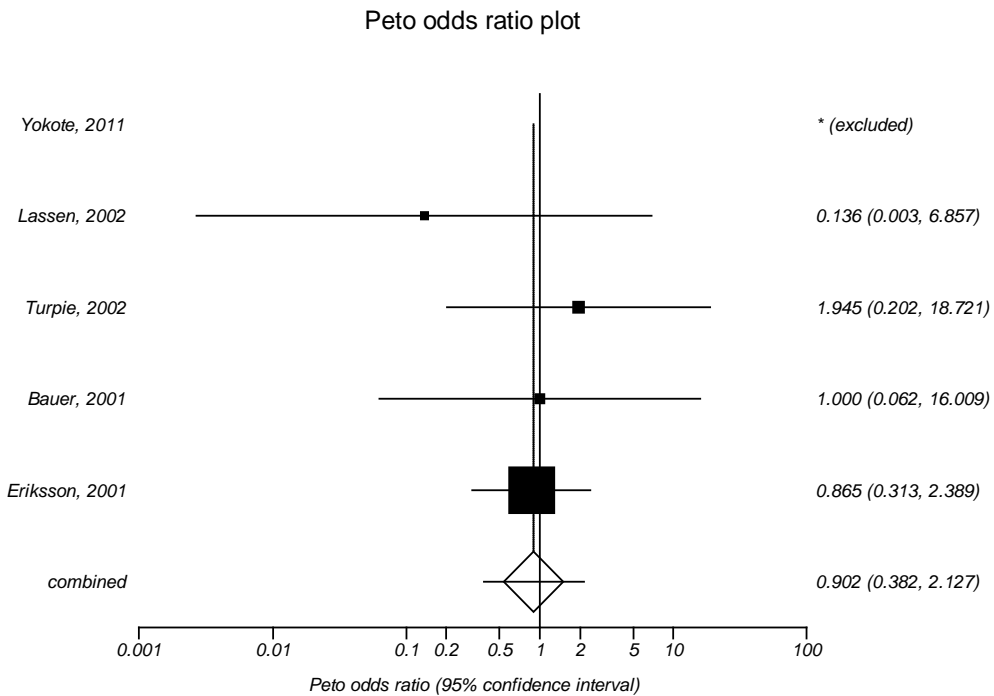


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

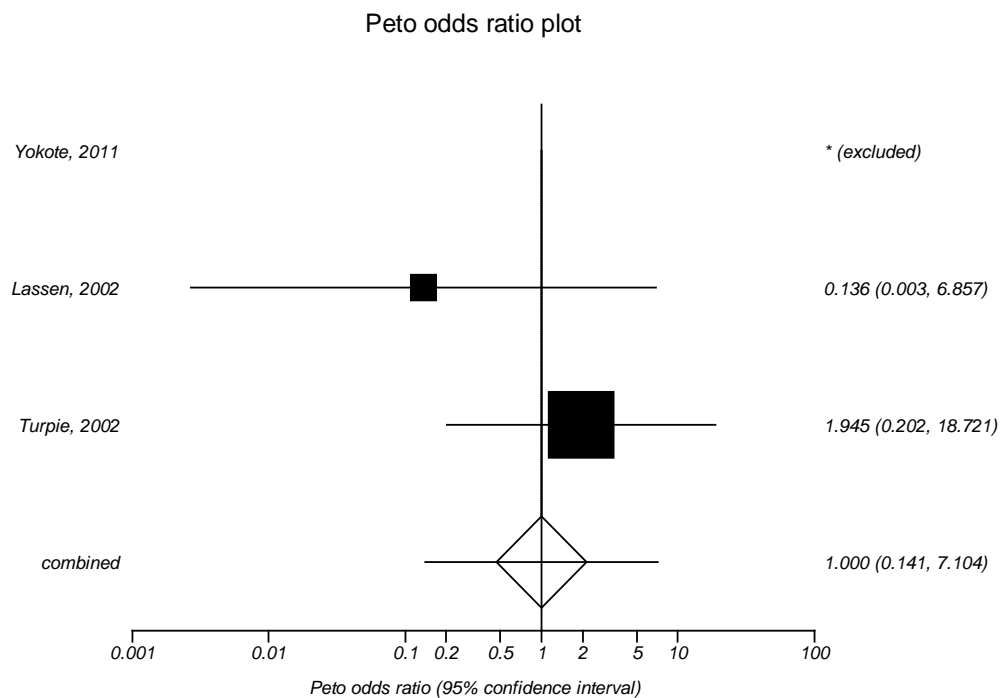
Figure 79. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on fatal pulmonary embolism in patients undergoing major orthopedic surgery (Same as analysis limited to trials published from 2001-present)



I^2 : 0 percent
 Egger's p-value: 0.744

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

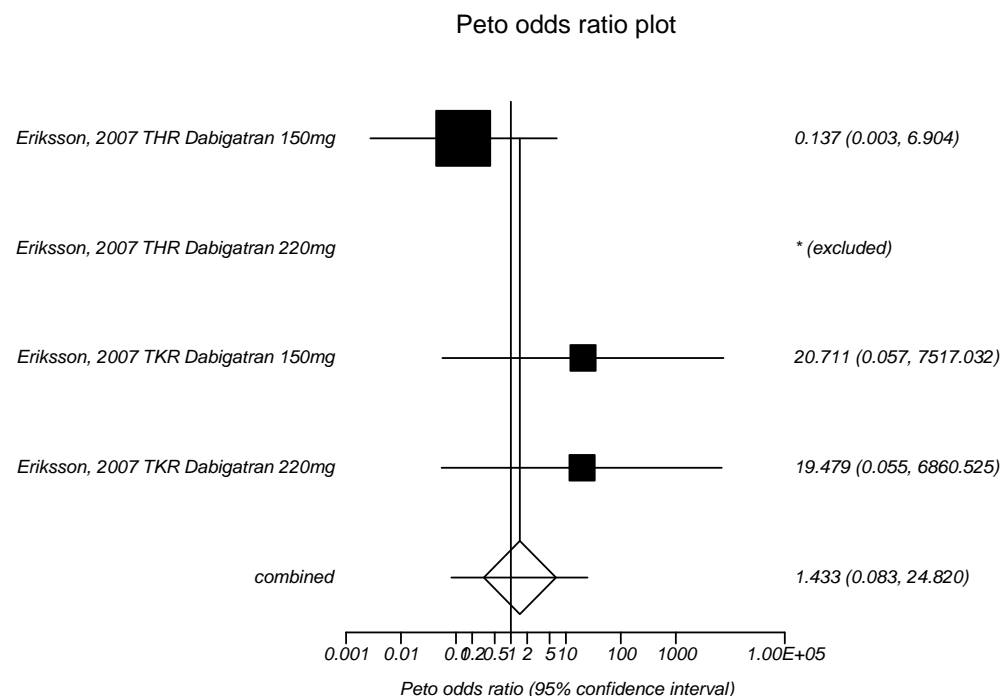
Figure 80. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on fatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 81. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on fatal pulmonary embolism in patients undergoing major orthopedic surgery (Same as analysis limited to trials published from 2001-present)

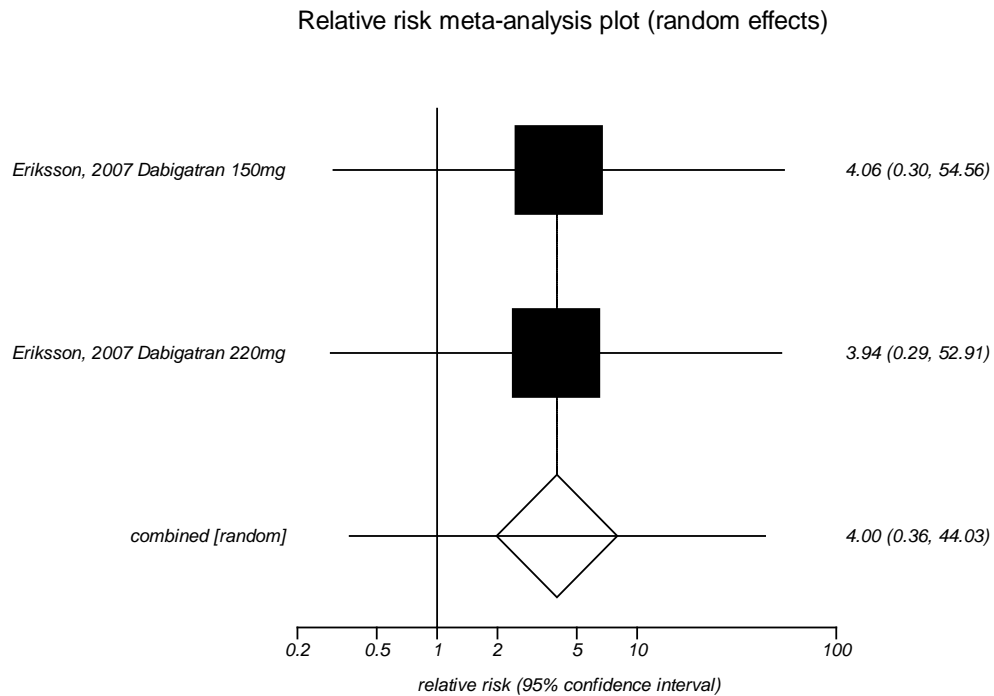


I^2 : 31.7 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

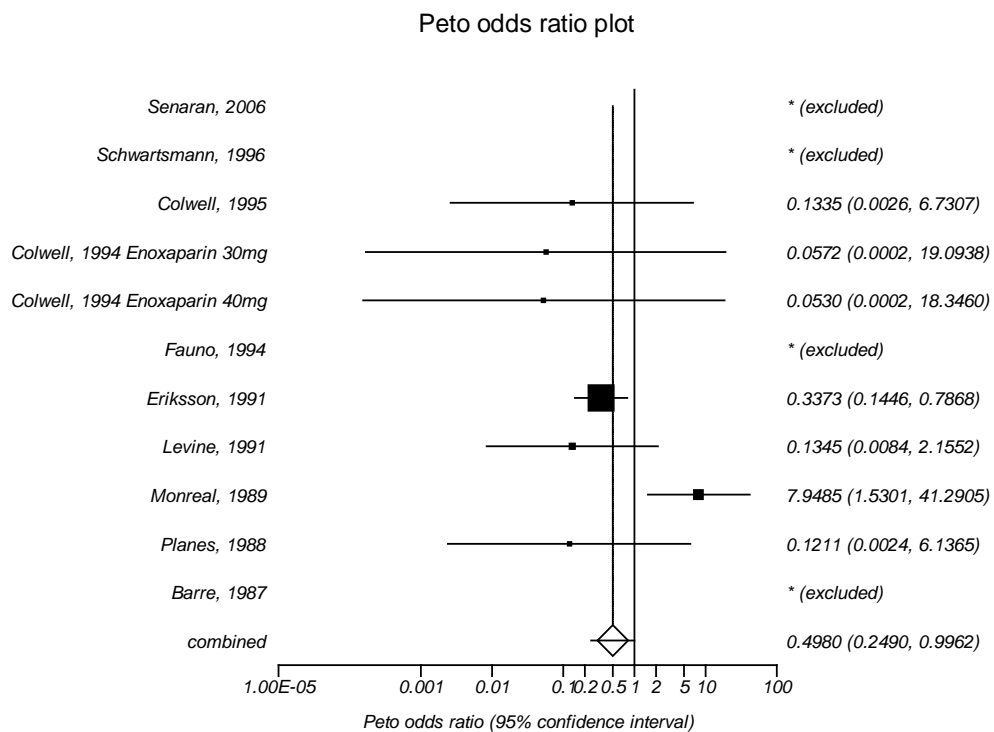
Figure 82. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on fatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total knee replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

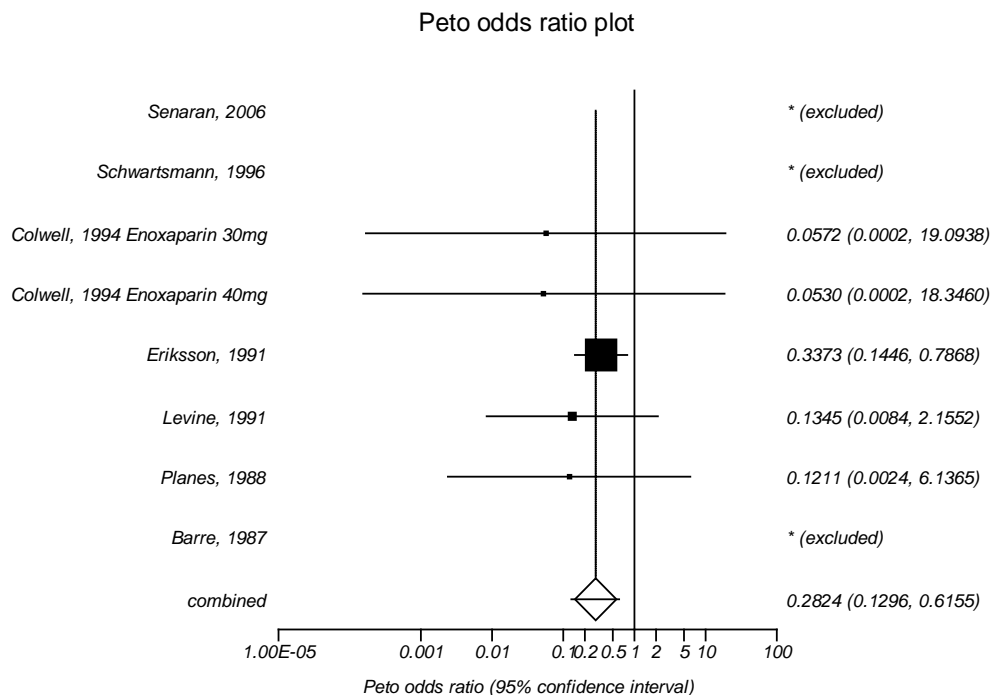
Figure 83. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery



I^2 : 58.8 percent
 Egger's p-value: 0.634

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

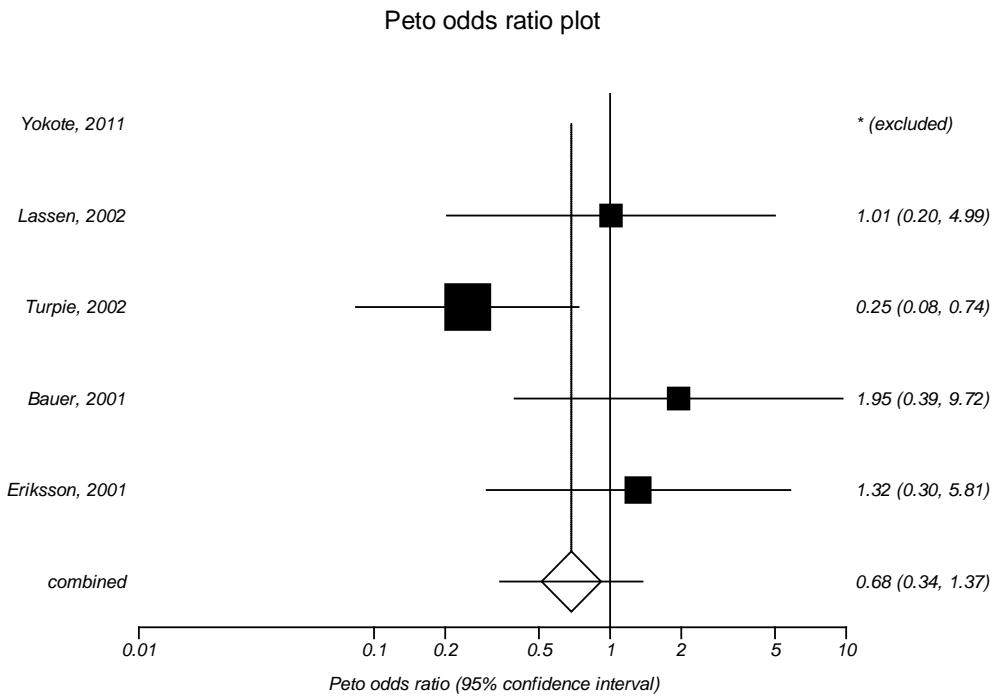
Figure 84. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

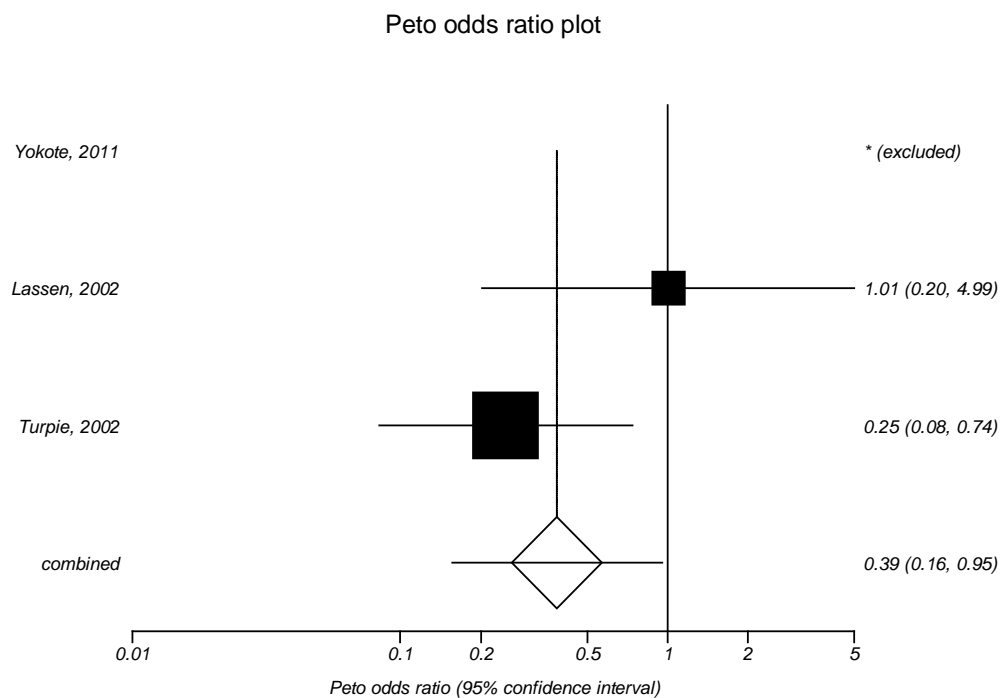
Figure 85. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)



I^2 : 49.5 percent
 Egger's p-value: 0.040

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

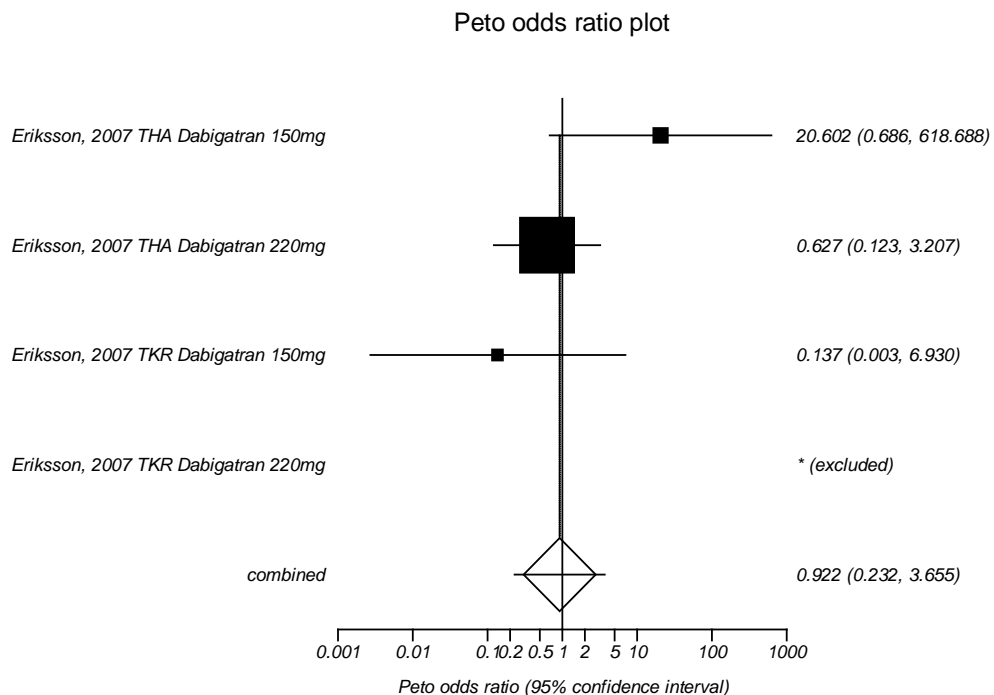
Figure 86. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 87. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001 to the present)

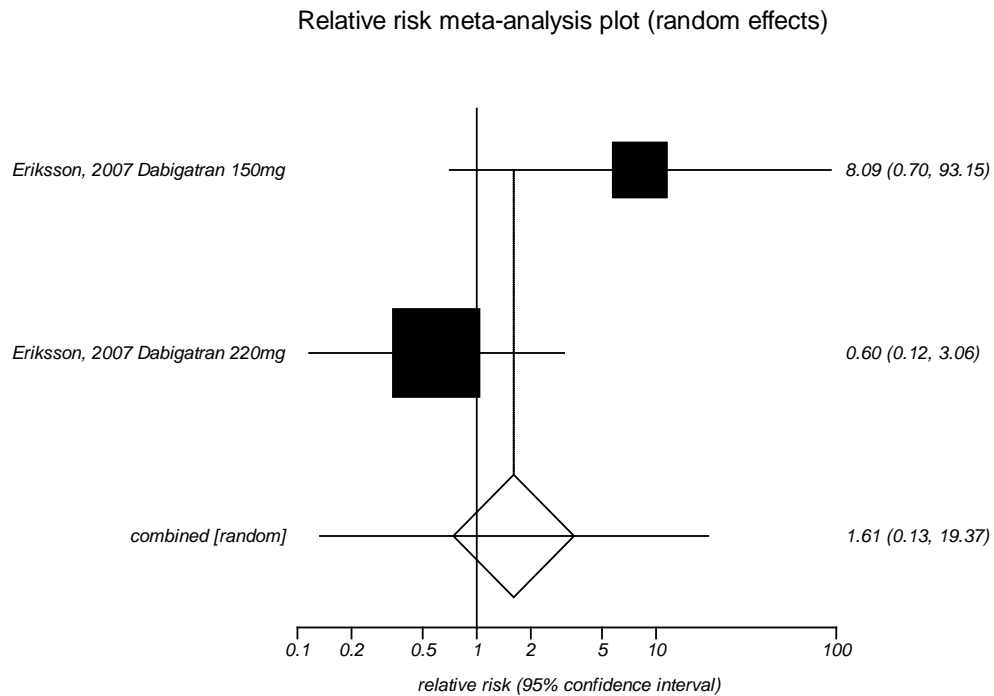


I^2 : 53.7 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

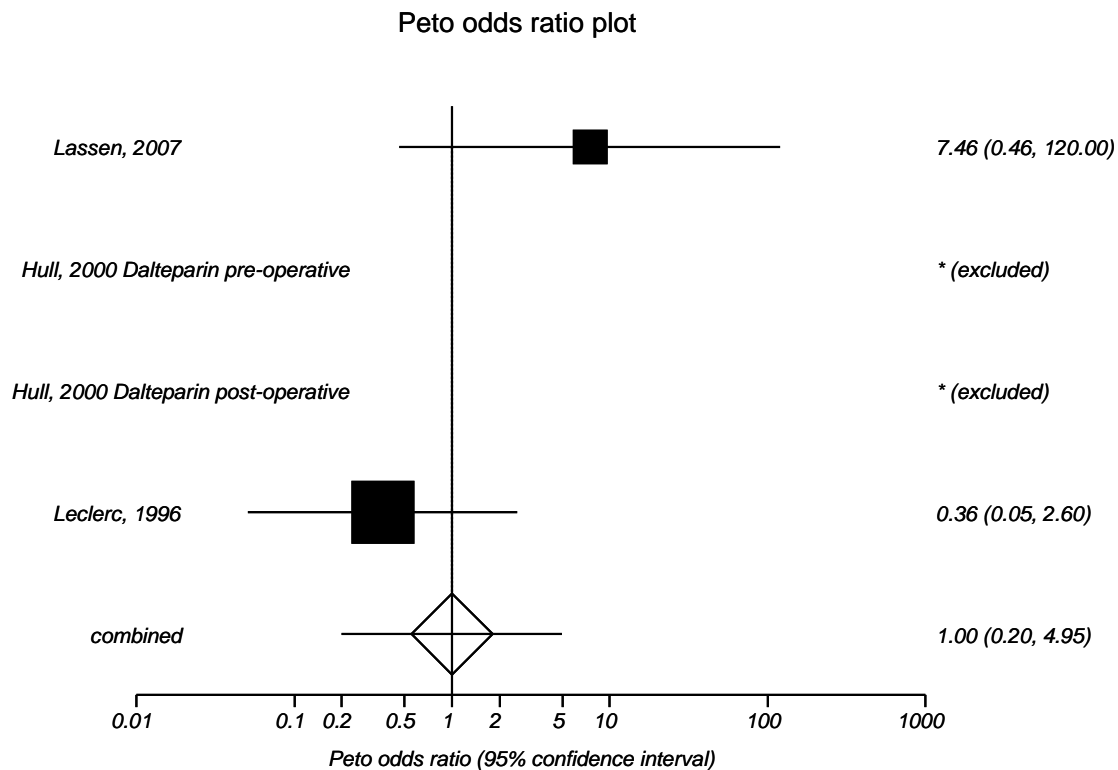
Figure 88. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 89. Impact of injectable low molecular weight heparin versus oral vitamin k antagonists on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery

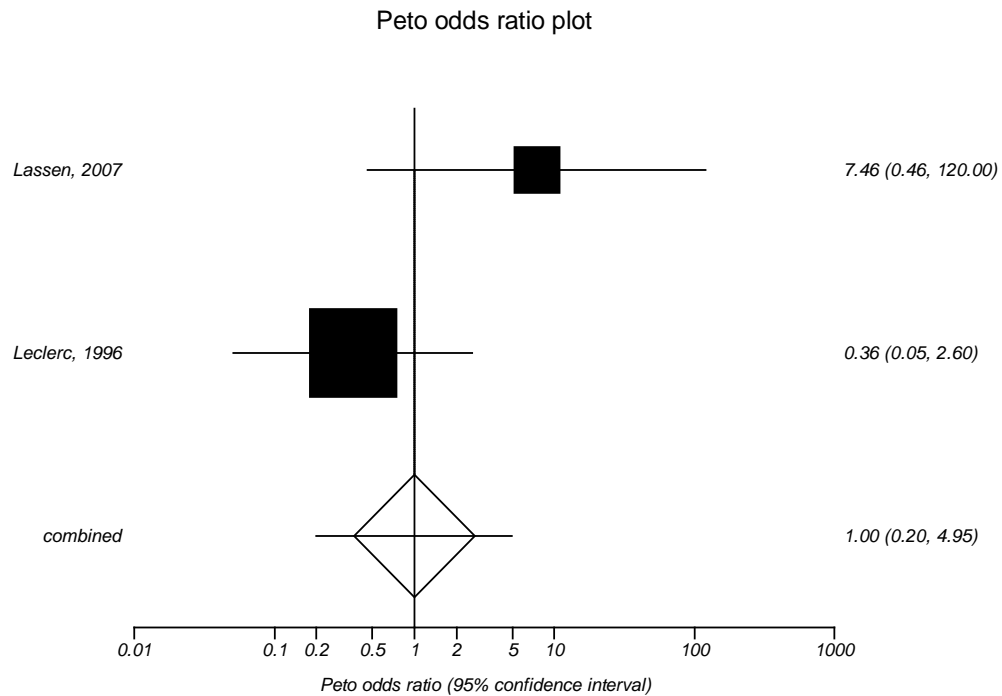


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

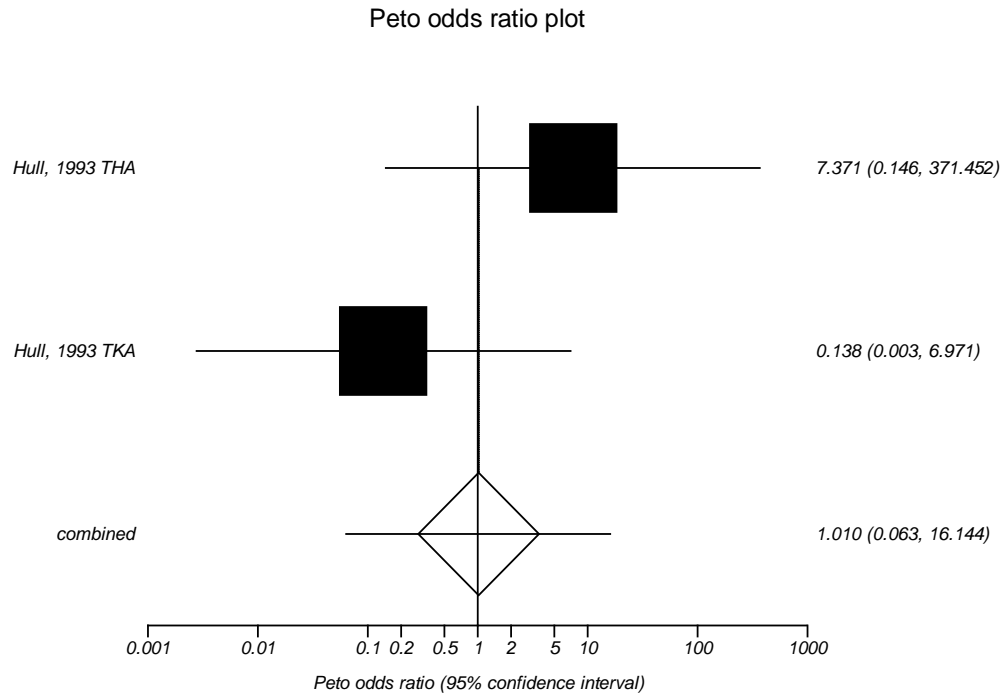
Figure 90. Impact of injectable low molecular weight heparin versus oral vitamin k antagonists on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 91. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on nonfatal pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery

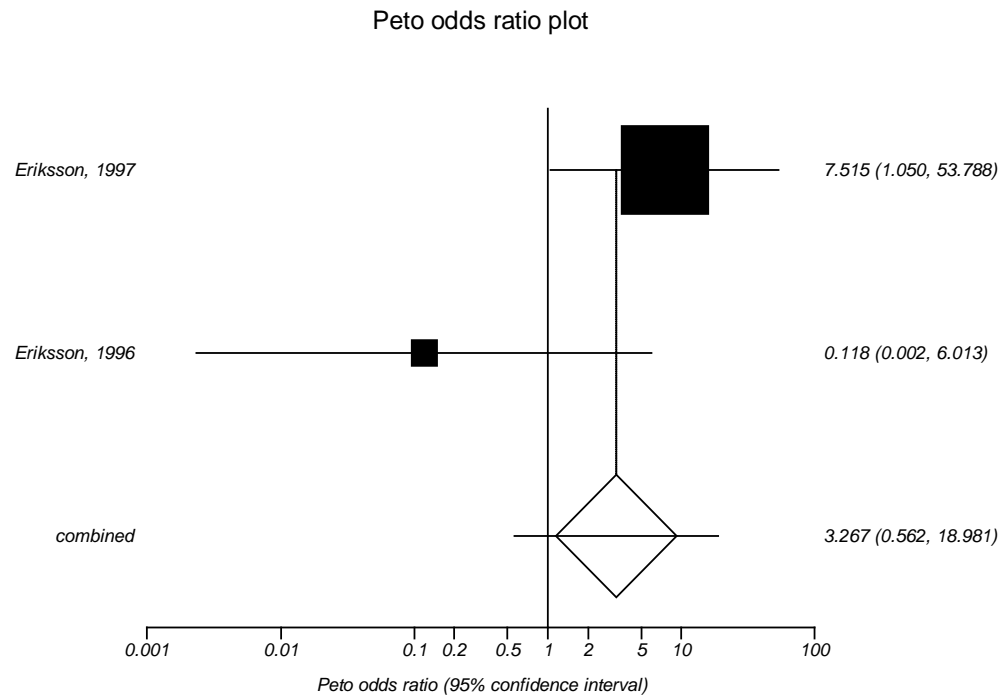


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 92. Impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on nonfatal pulmonary embolism in patients undergoing major orthopedic surgery (same as analysis limited to total hip replacement)

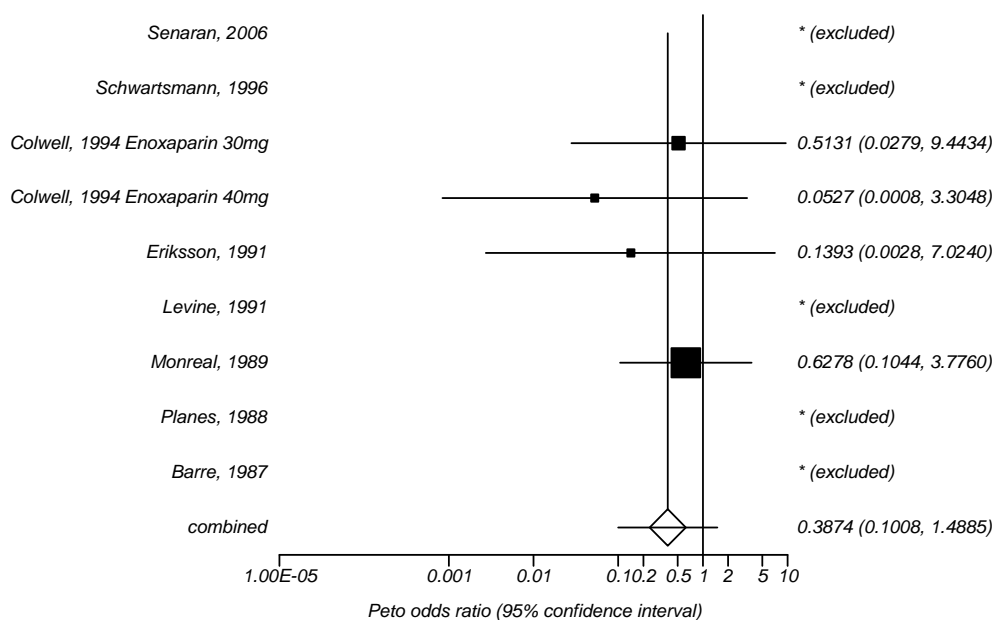


I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 93. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on mortality in patients who had major orthopedic surgery

Peto odds ratio plot

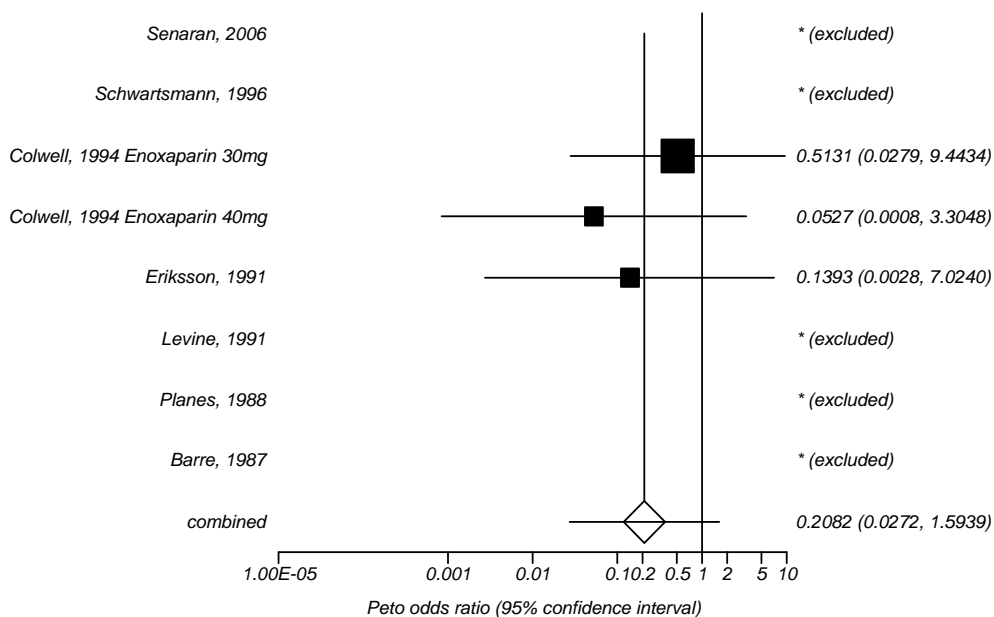


I^2 : 0 percent
Egger's p-value: 0.102

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 94. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on mortality in patients who had major orthopedic surgery limited to total hip replacement surgery

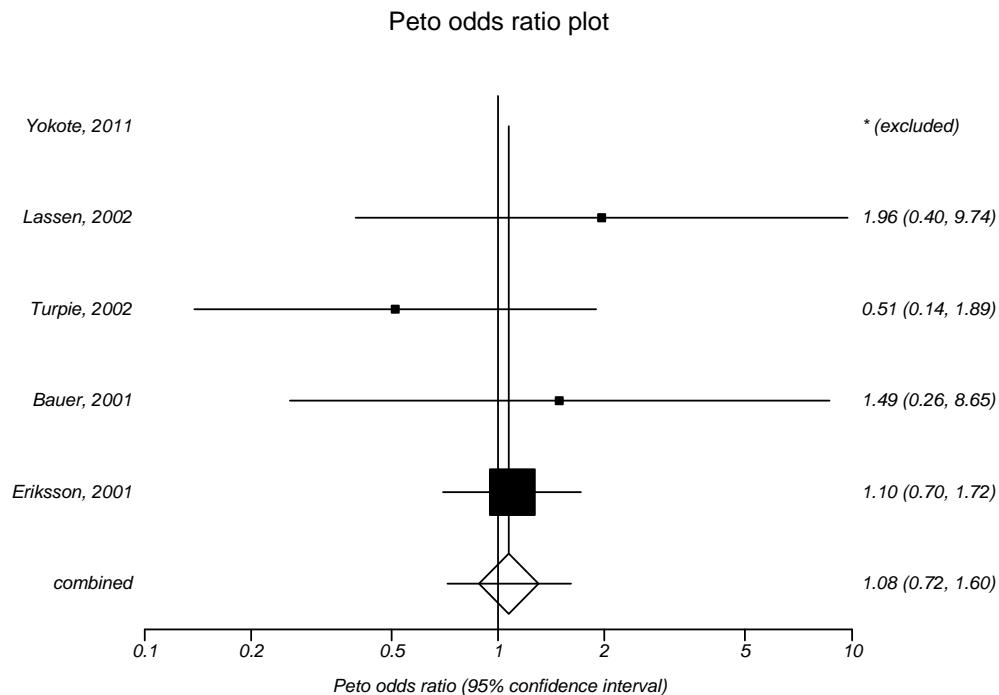
Peto odds ratio plot



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

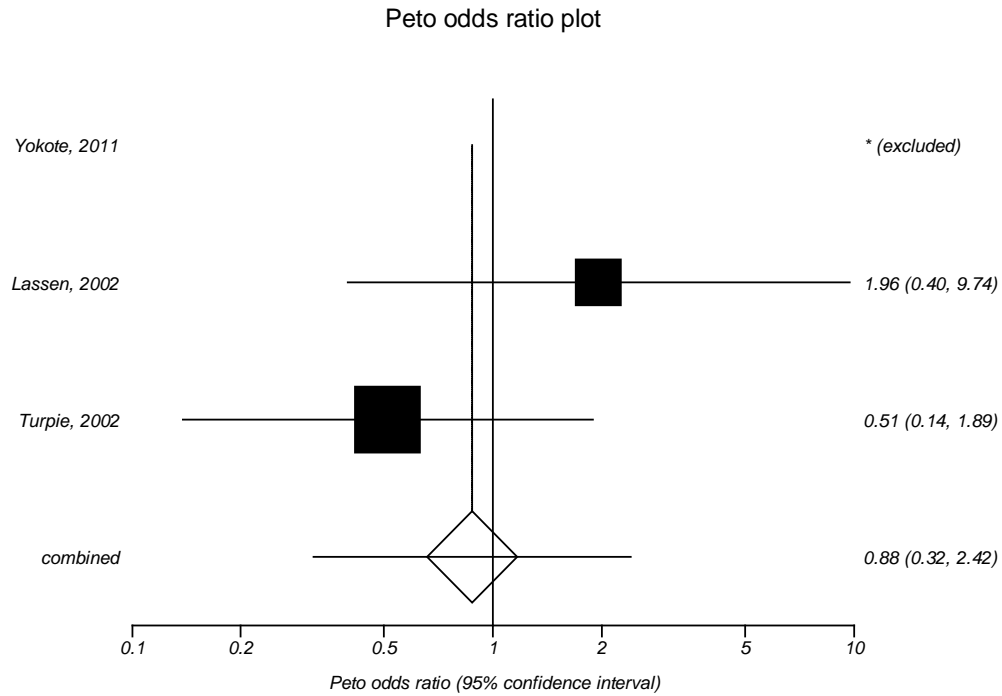
Figure 95. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery (same as analysis limited to 2001 to present)



I^2 : 0 percent
 Egger's p-value: $P = 0.952$

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 96. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery limited to total hip replacement surgery

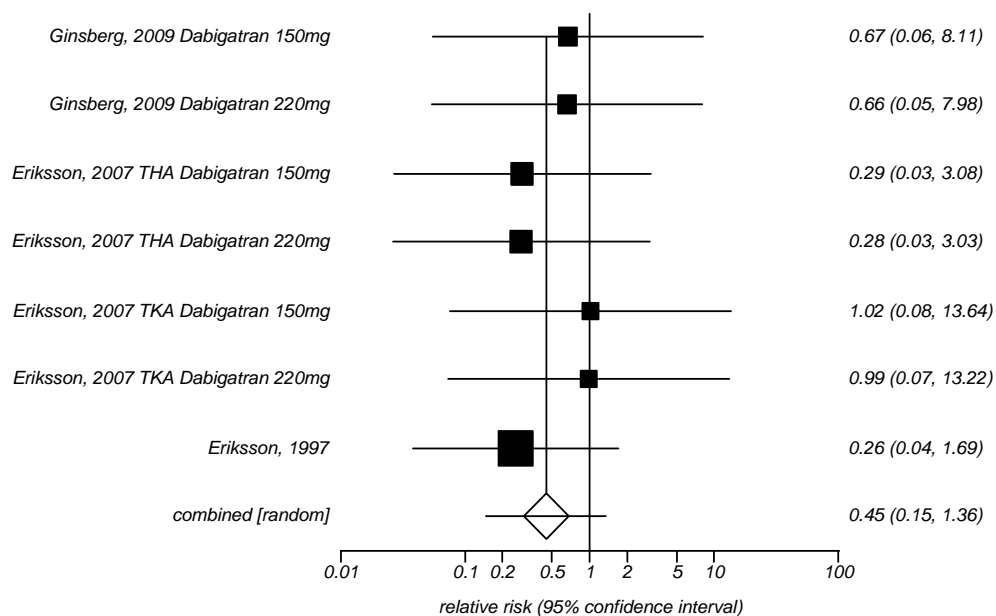


I²: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 97. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

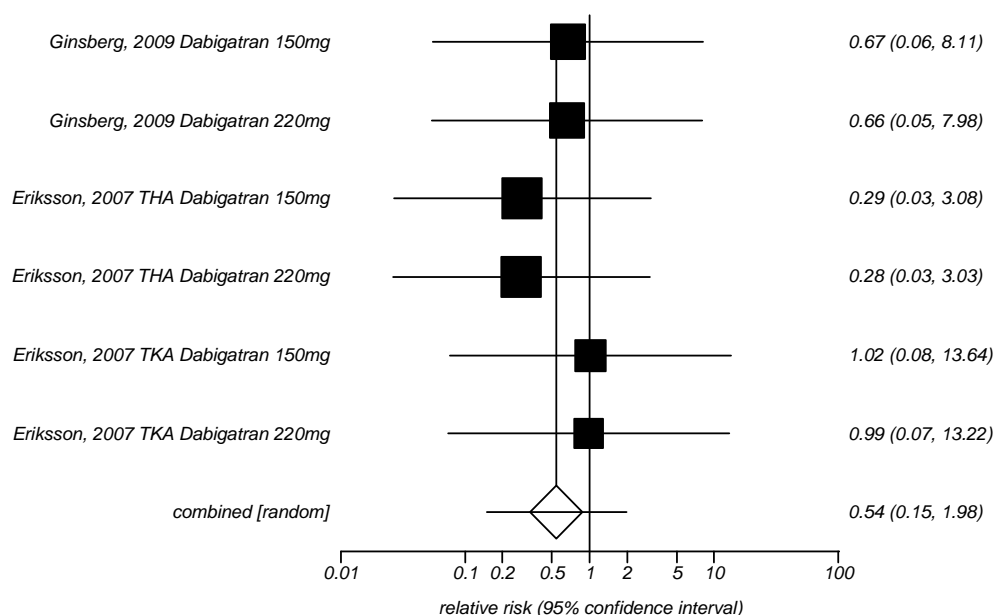


I^2 : 0 percent
Egger's p-value: $P = 0.023$

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 98. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality in patients who had major orthopedic surgery limited to trials published from 2001 to present

Relative risk meta-analysis plot (random effects)

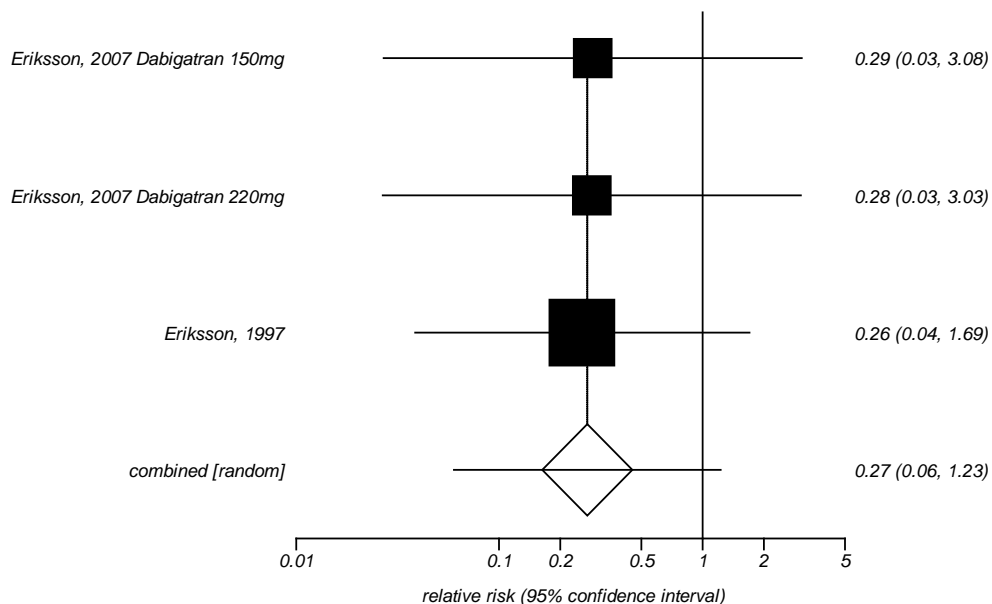


I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 99. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality in patients who had major orthopedic surgery limited to total hip replacement surgery

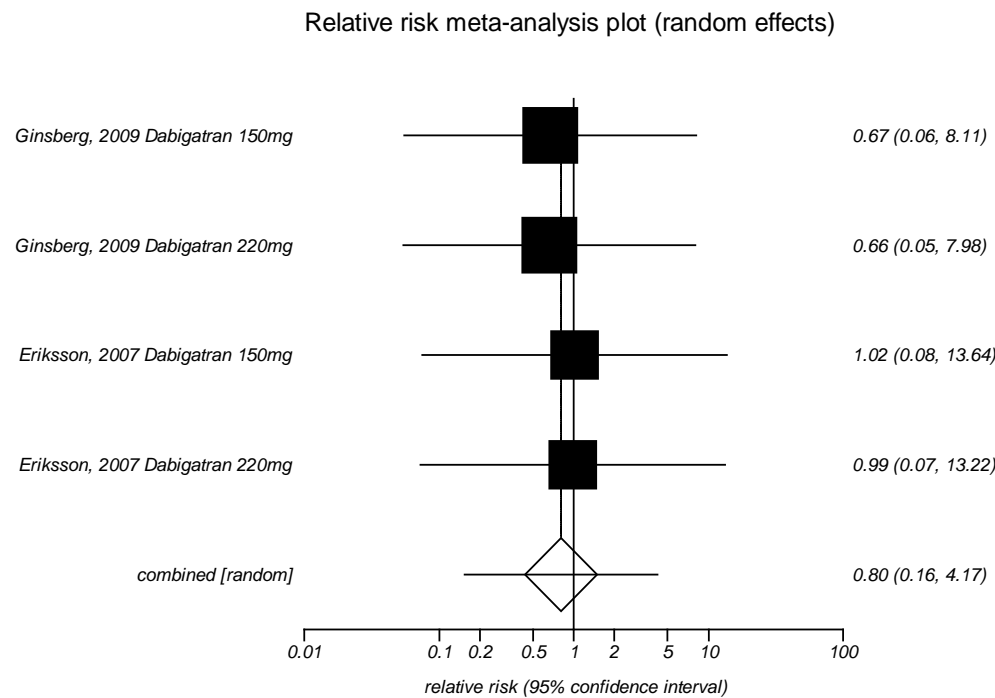
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

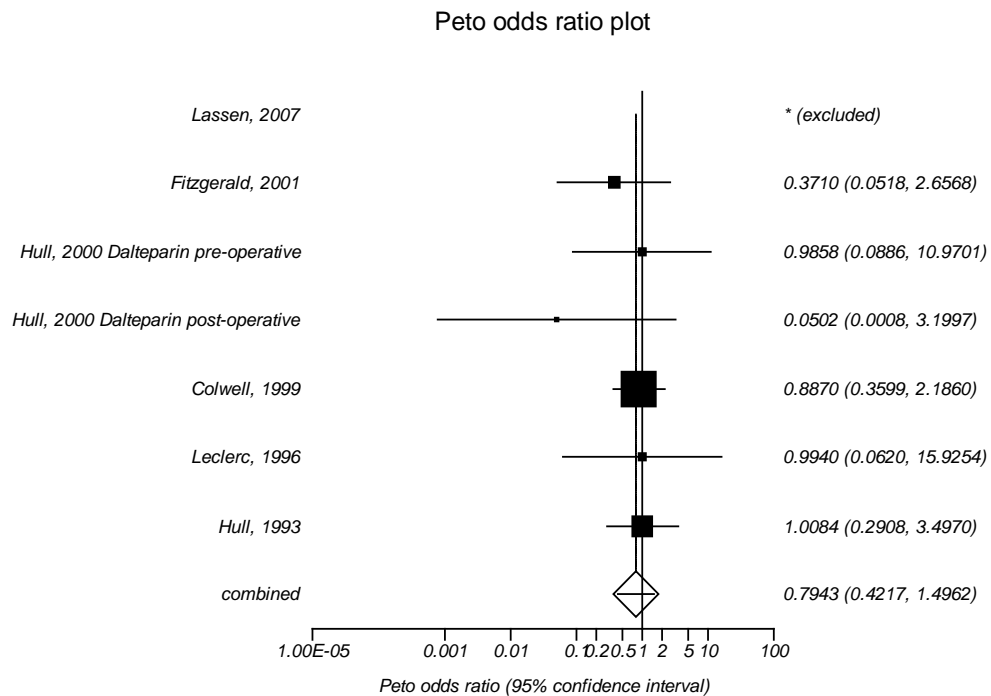
Figure 100. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality in patients who had major orthopedic surgery limited to total knee replacement surgery



I²: 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

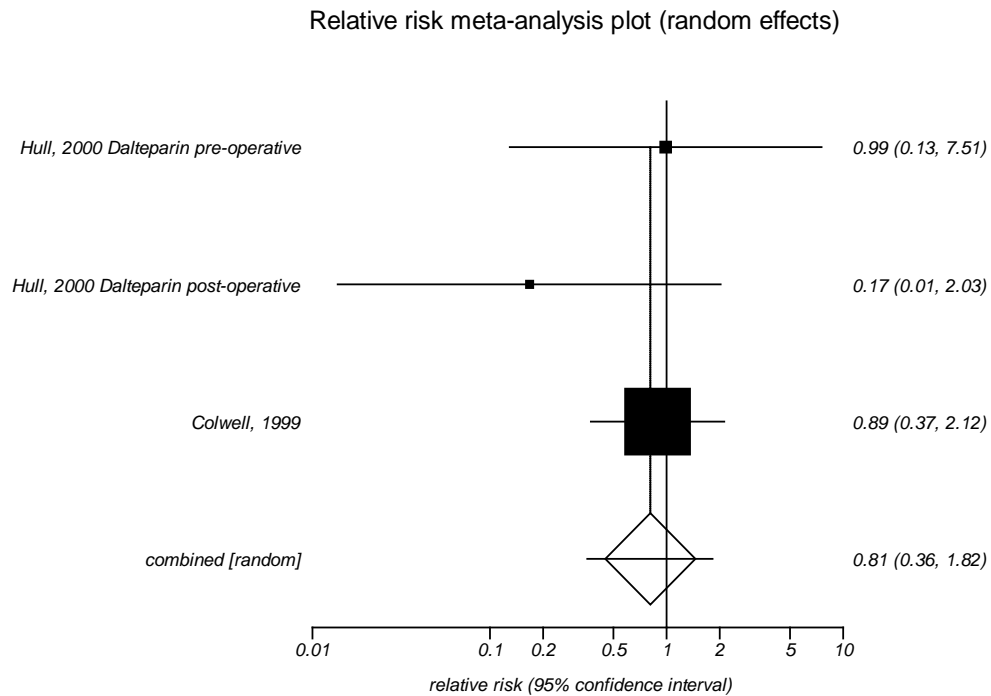
Figure 101. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on mortality in patients who had major orthopedic surgery



I^2 : 0 percent
 Egger's p-value: $P = 0.188$

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

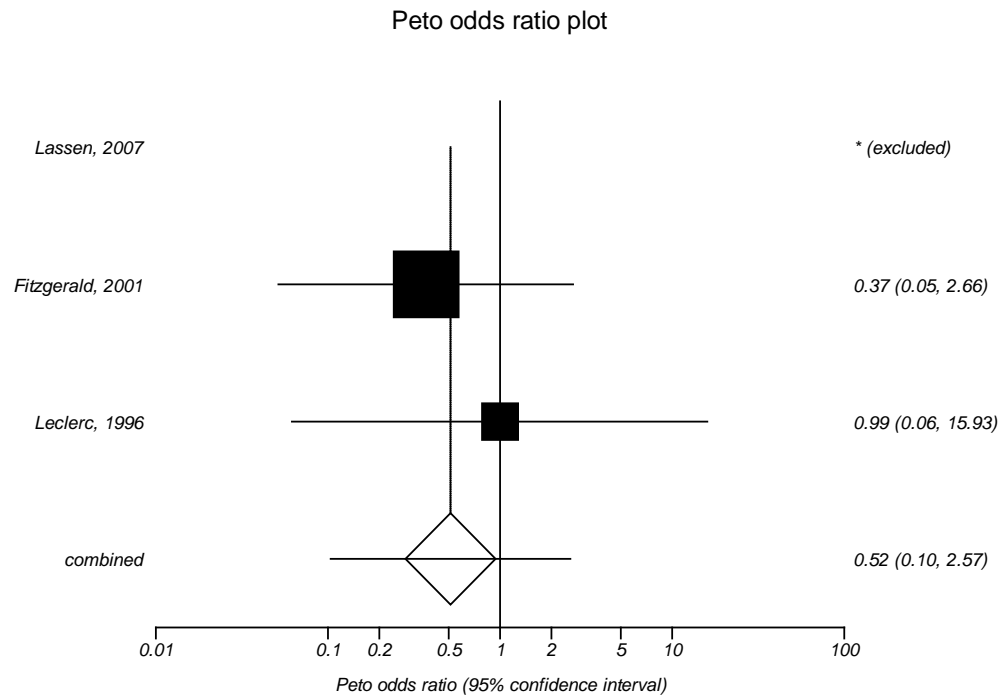
Figure 102. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on mortality in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

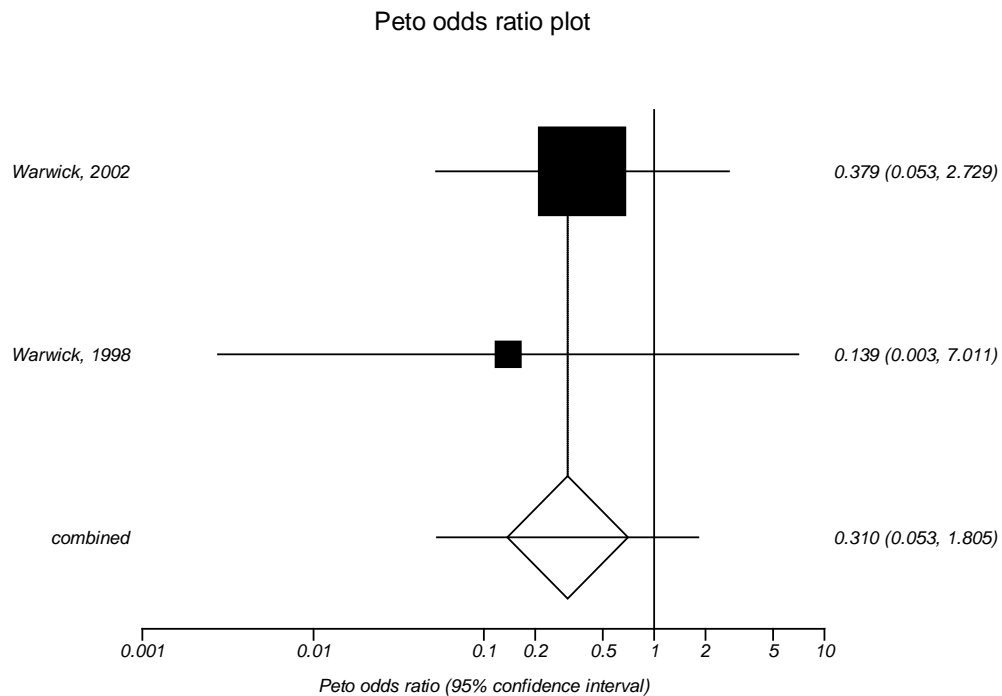
Figure 103. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on mortality in patients who had major orthopedic surgery limited to total knee replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 104. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery

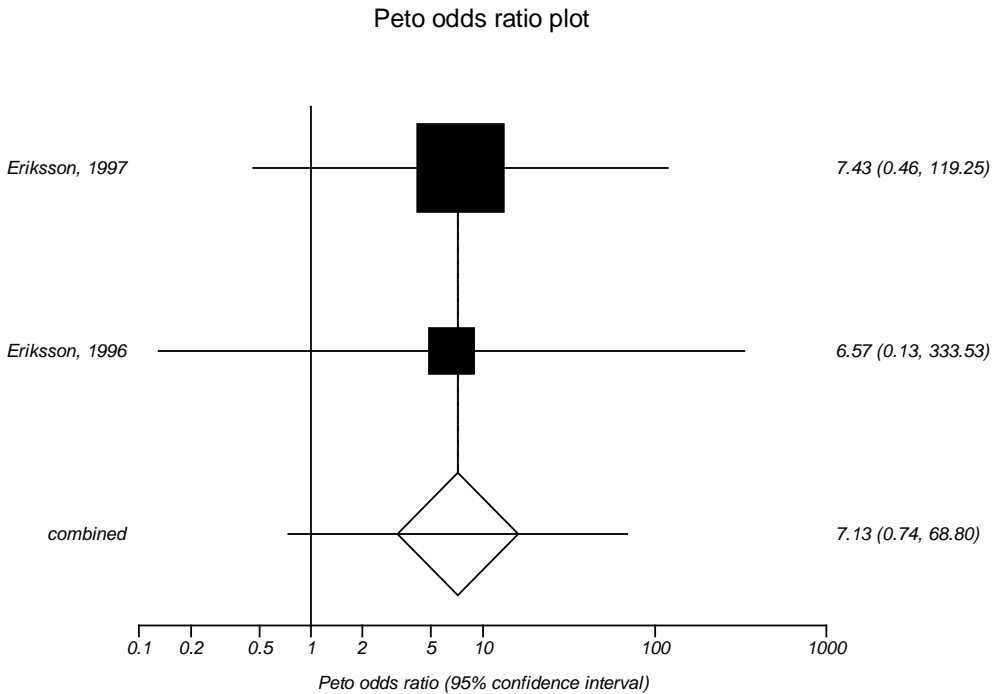


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 105. Impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality in patients who had major orthopedic surgery (same as analysis limited to total hip replacement surgery)



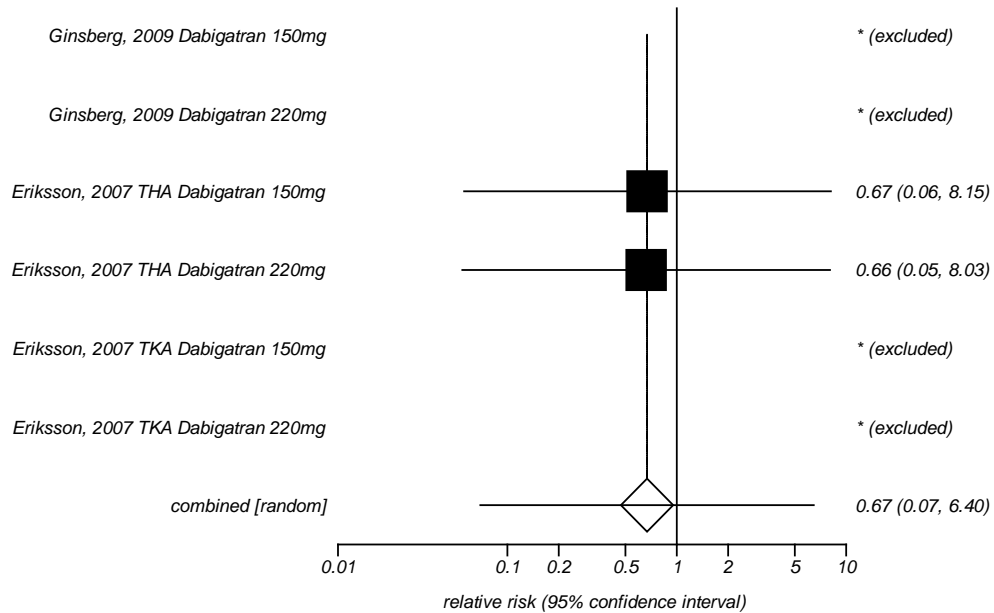
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 106. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery (same as analysis limited to 2001 to present)

Relative risk meta-analysis plot (random effects)



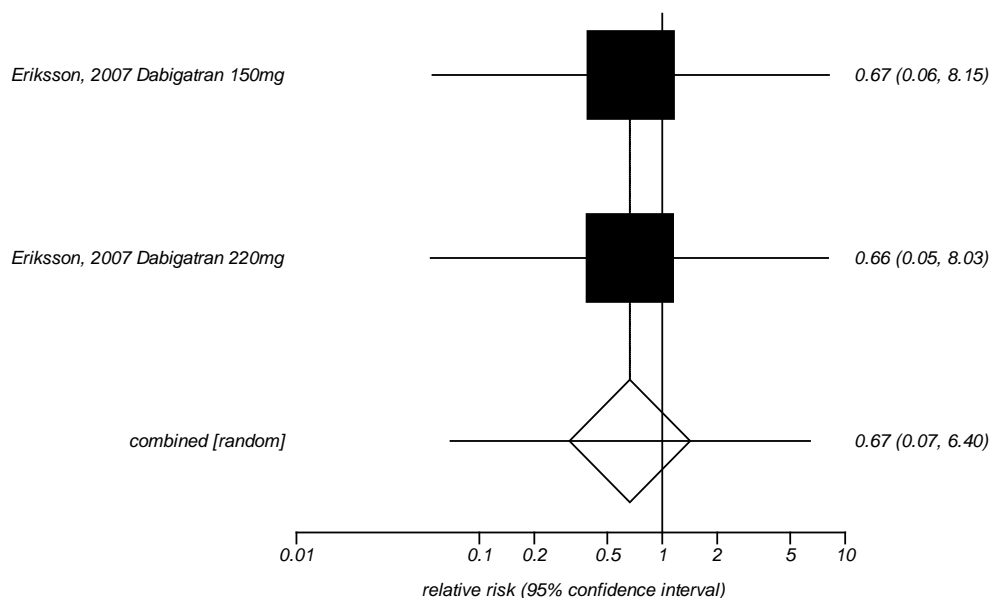
I²: Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 107. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery limited to total hip replacement surgery

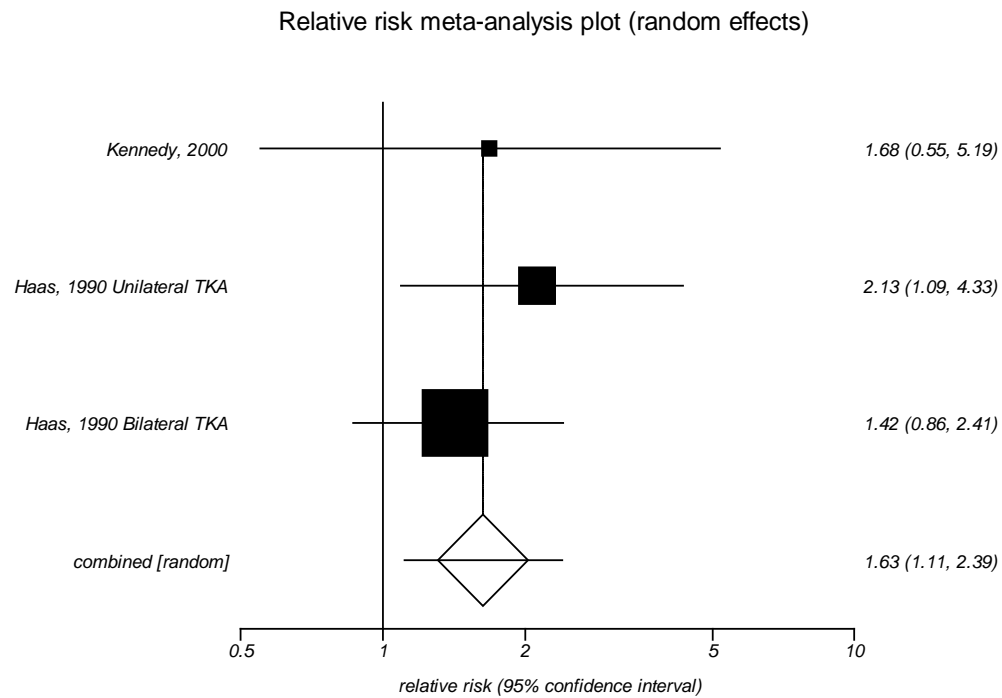
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 108. Impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery

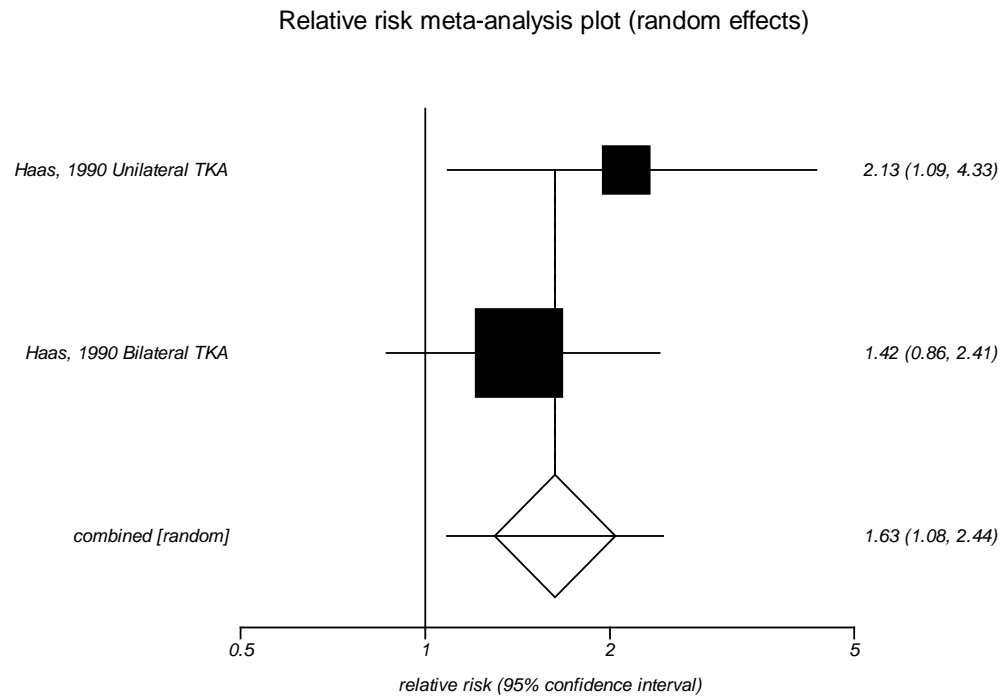


I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

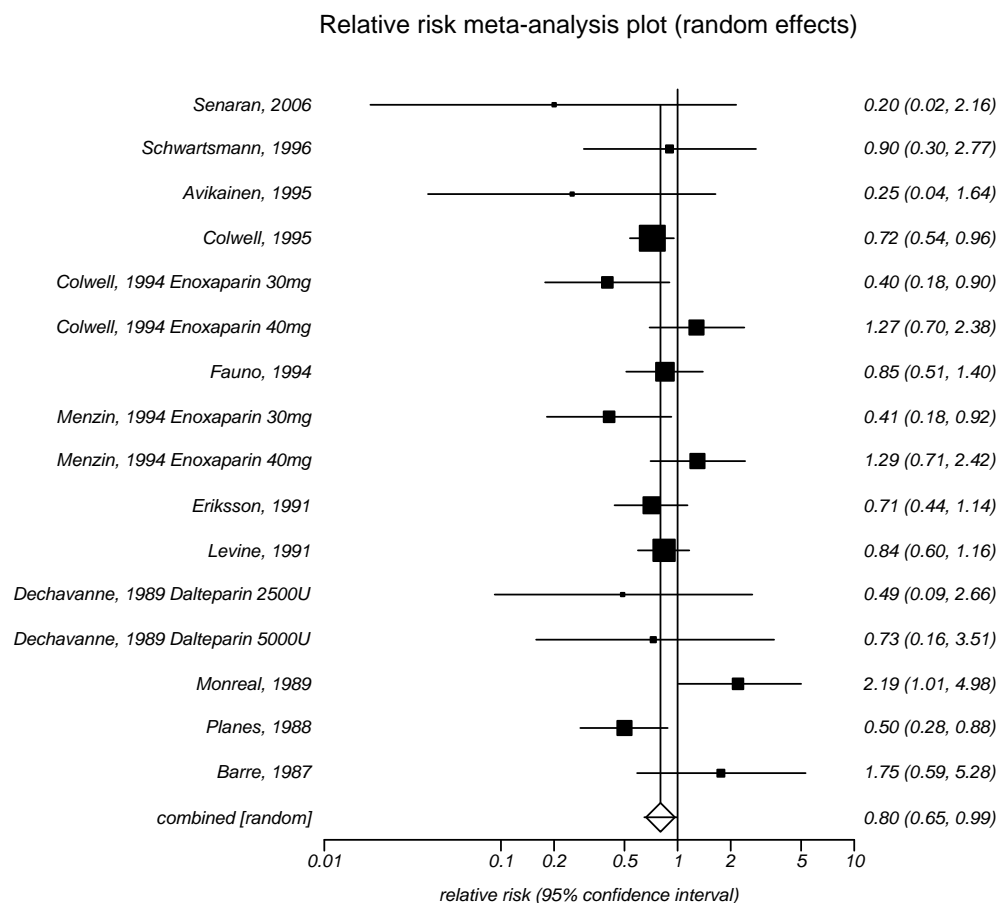
Figure 109. Impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

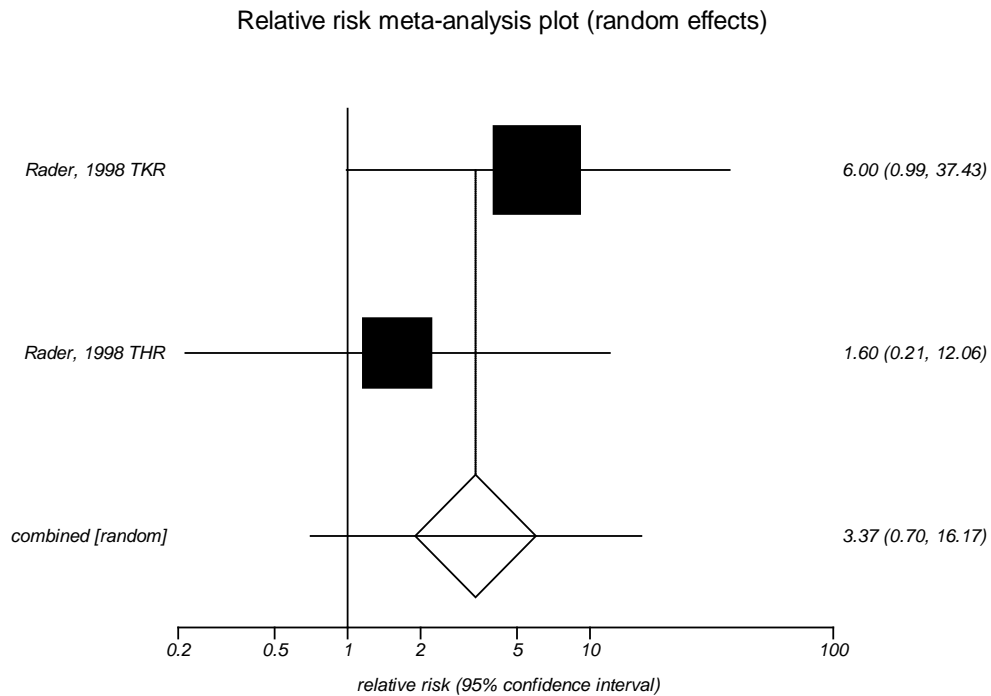
Figure 110. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery



I^2 : 34.4 percent
Egger's p-value: 0.808

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 111. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on deep vein thrombosis in patients who all received unfractionated heparin before randomization and underwent major orthopedic surgery

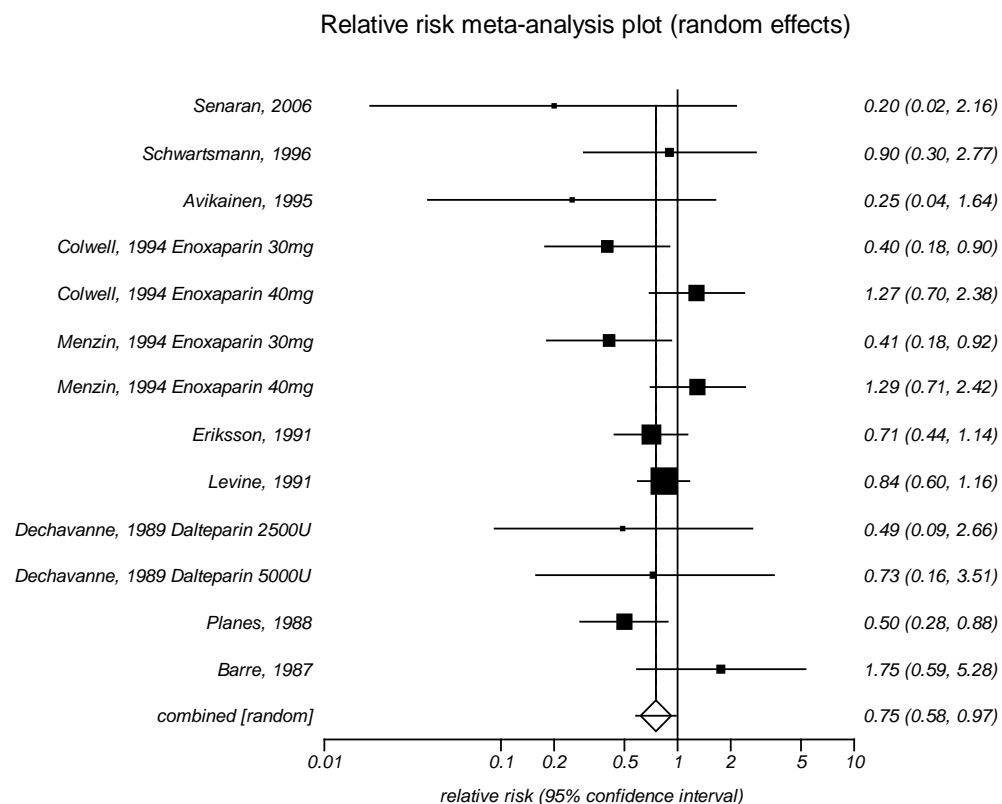


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

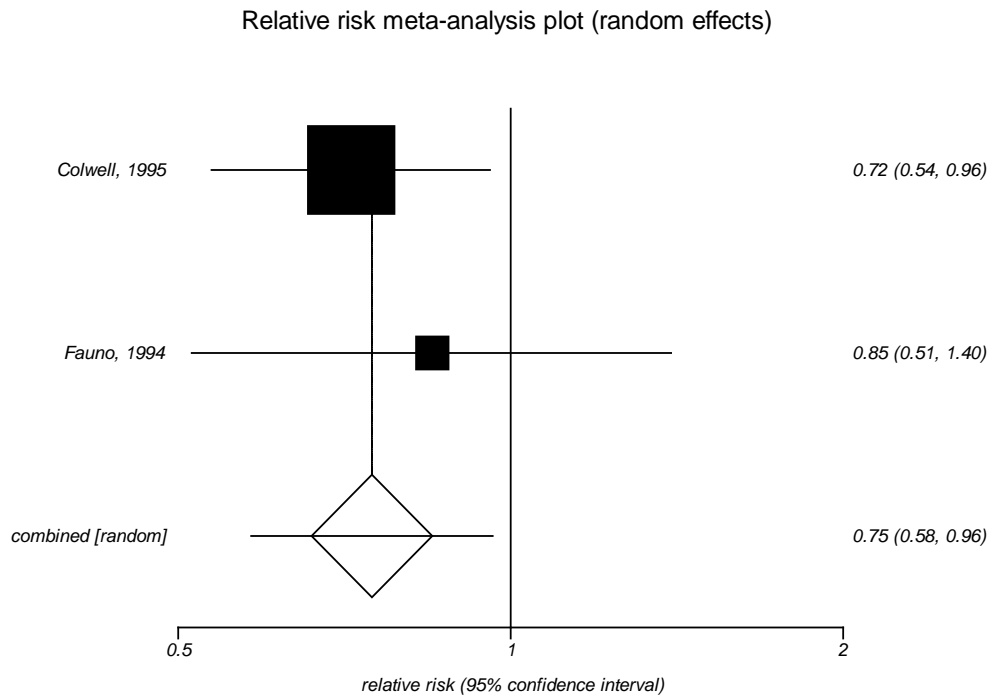
Figure 112. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 26.4 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

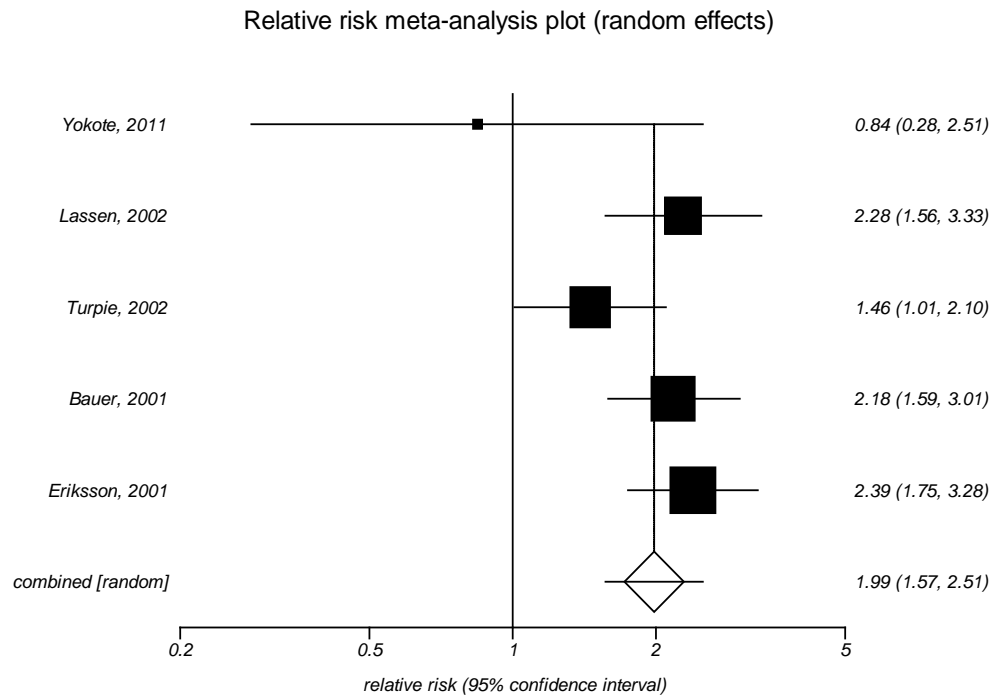
Figure 113. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

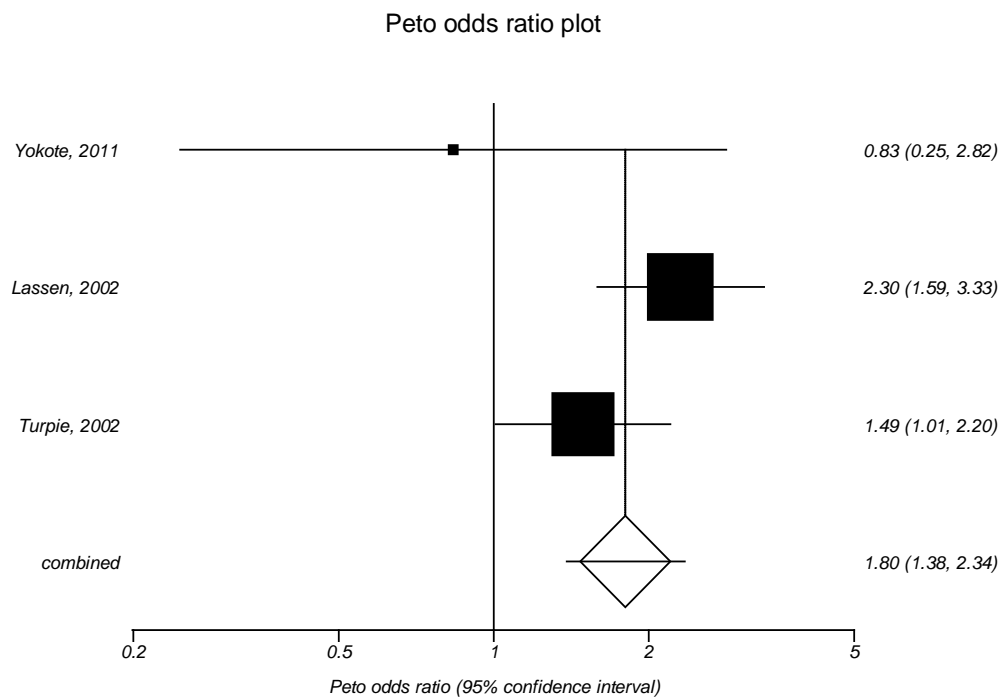
Figure 114. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited from 2001 to present)



I^2 : 42.5 percent
Egger's p-value: 0.225

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 115. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery

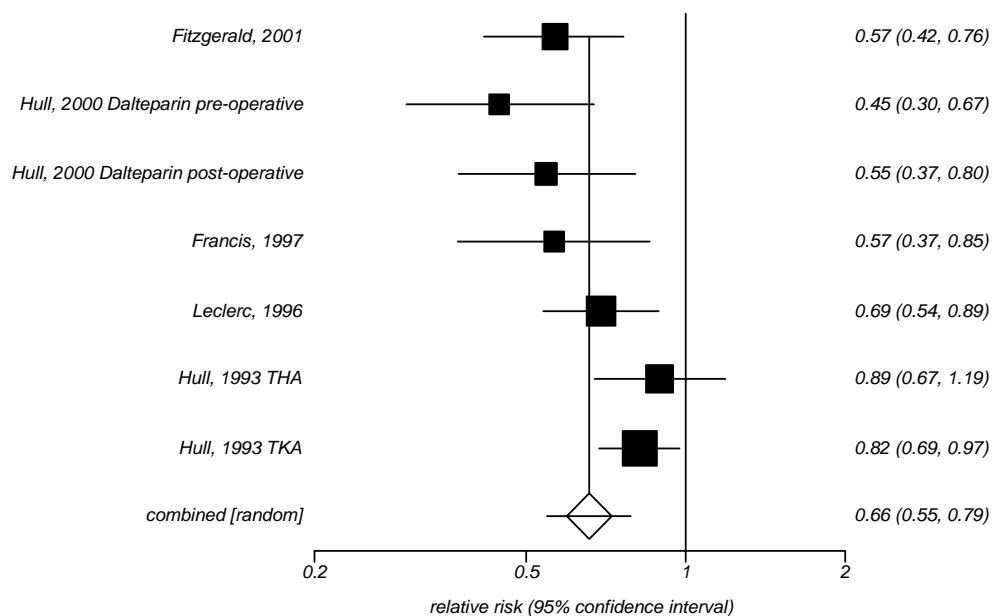


I^2 : 51.4 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 116. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery

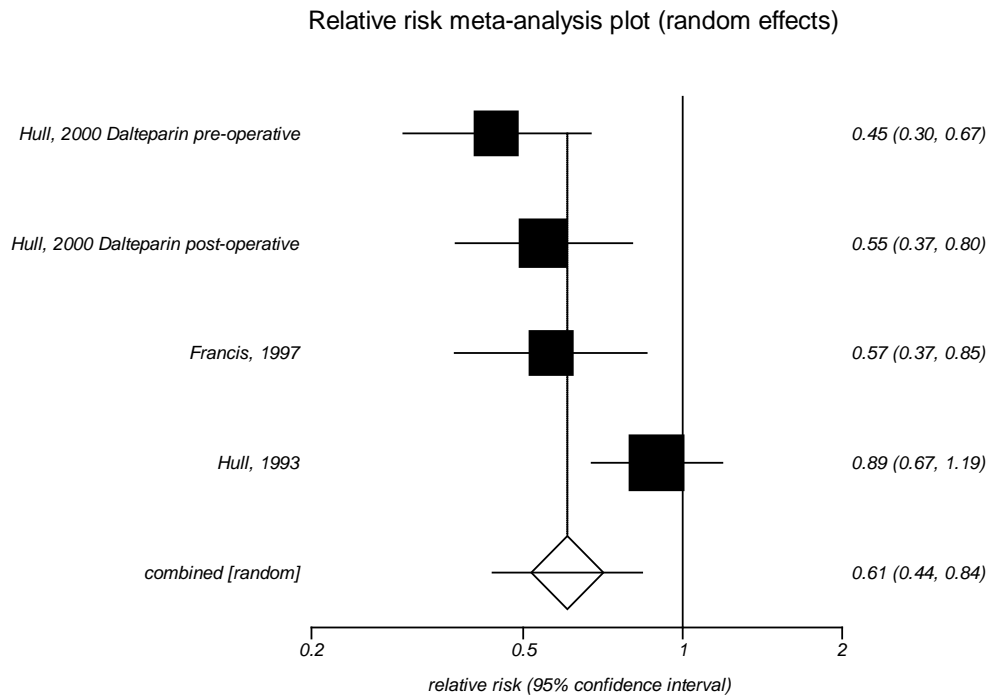
Relative risk meta-analysis plot (random effects)



I^2 : 60.9 percent
Egger's p-value: 0.033

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

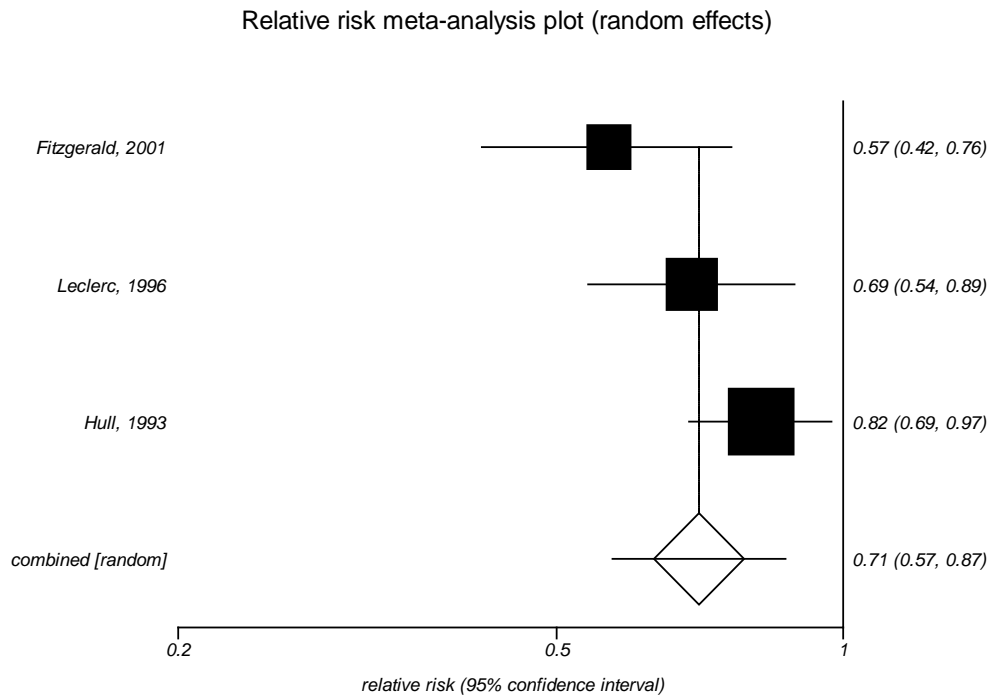
Figure 117. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 67.6 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

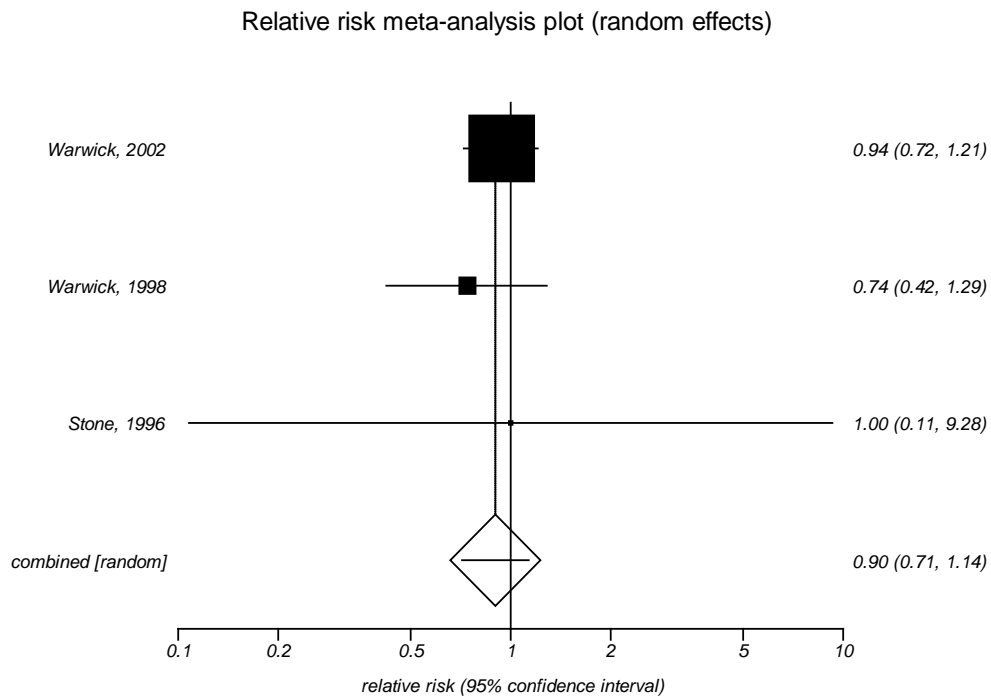
Figure 118. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 57.2 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 119. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery

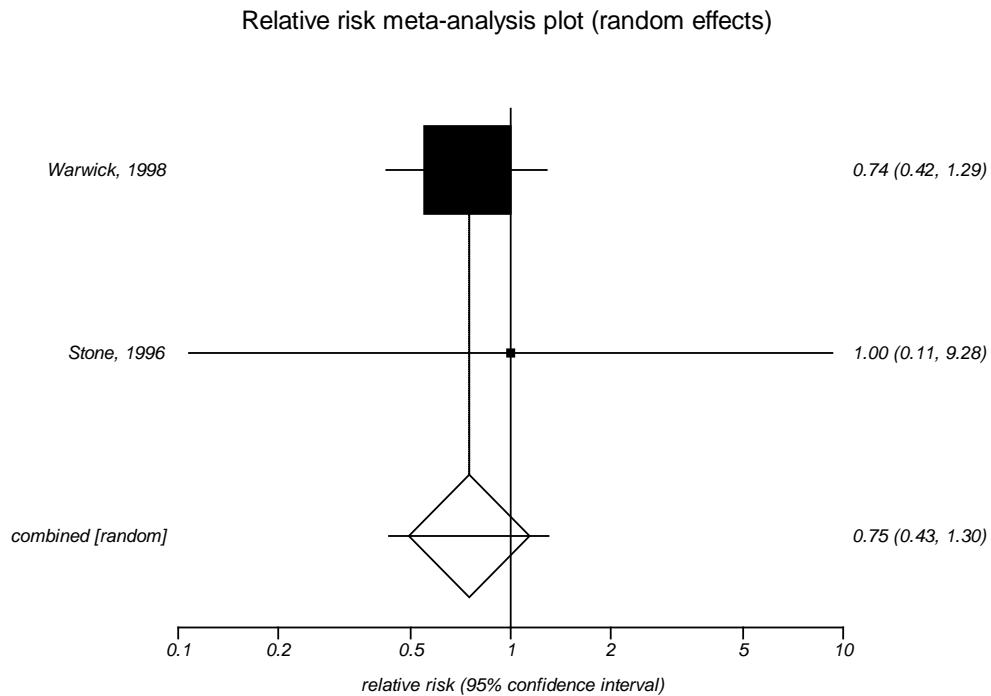


I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

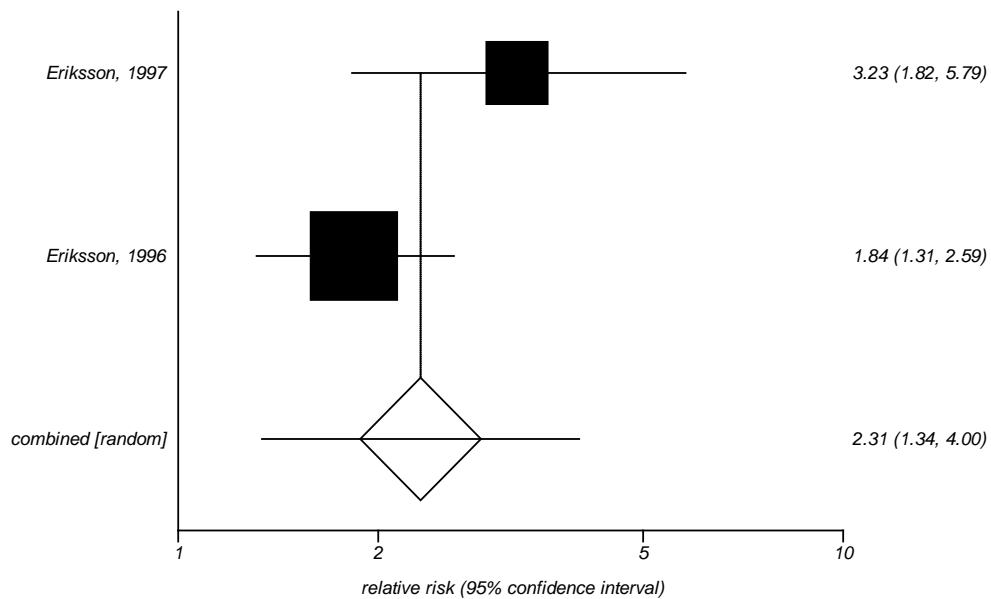
Figure 120. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 121. Impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery (same as total hip replacement therapy)

Relative risk meta-analysis plot (random effects)

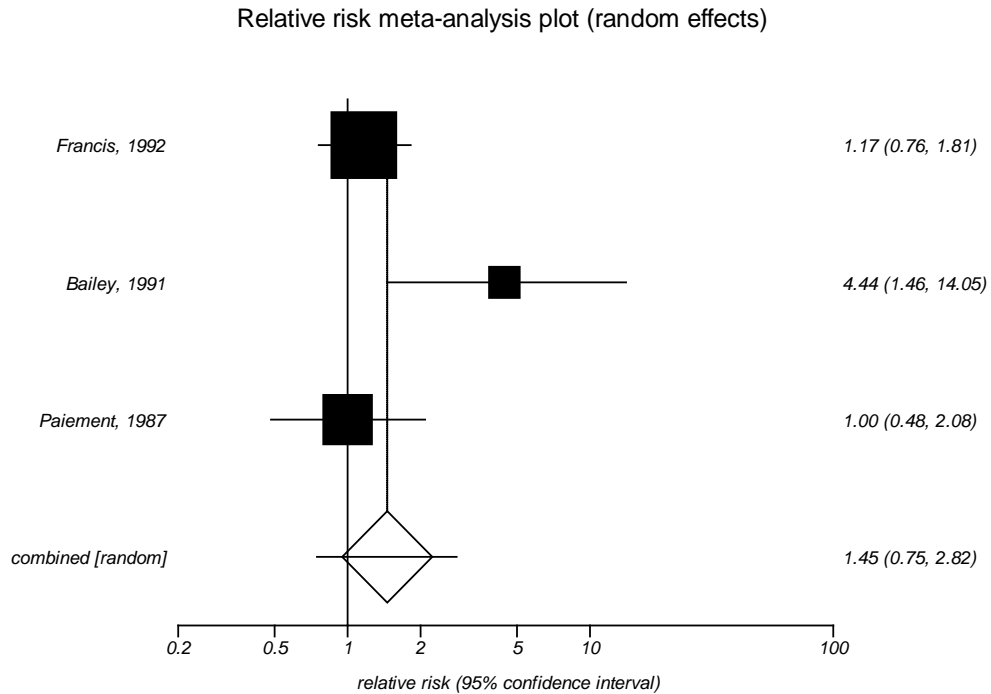


I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 122. Impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited to total hip replacement surgery)

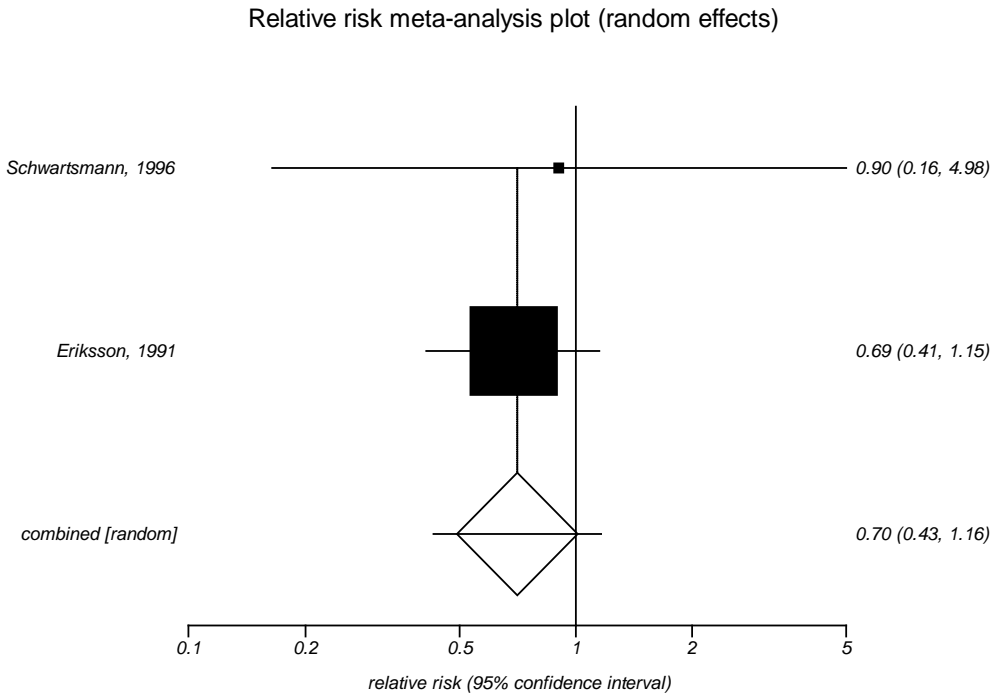


I^2 : 58.5 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

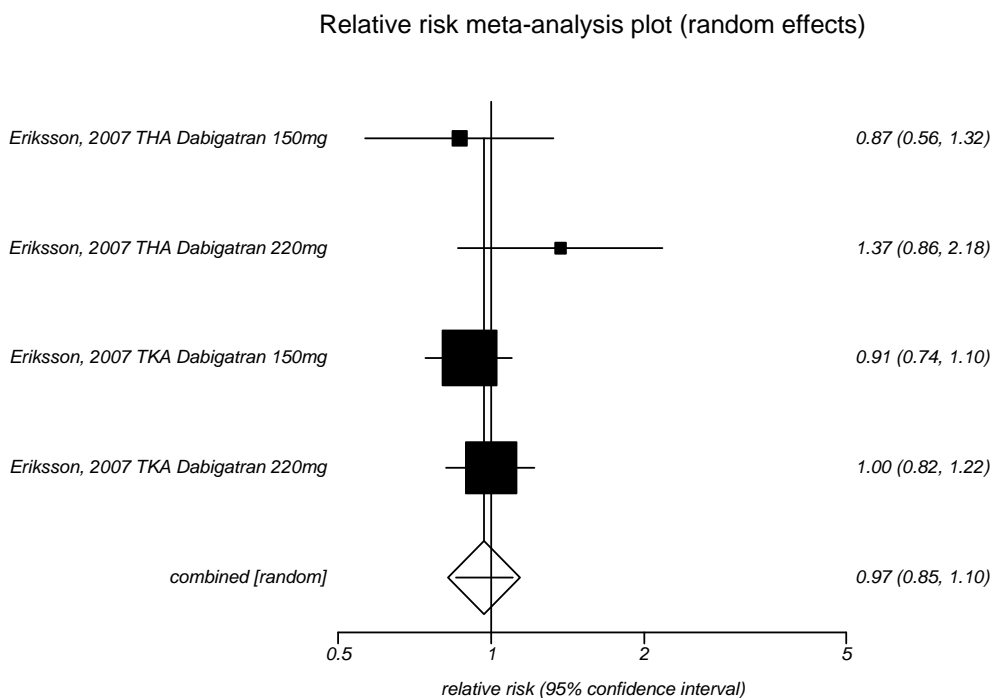
Figure 123. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on asymptomatic deep vein thrombosis in patients undergoing major orthopedic surgery (same as analysis limited to total hip replacement surgery)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

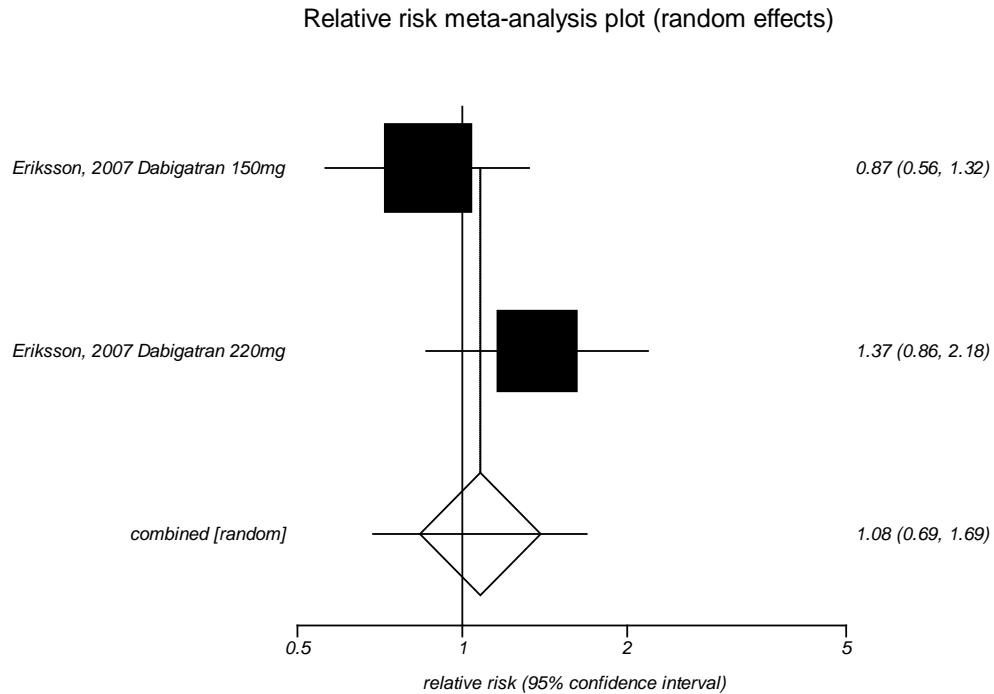
Figure 124. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on asymptomatic deep vein thrombosis in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)



I^2 : 0 percent
Egger's p-value: 0.536

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 125. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on asymptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery

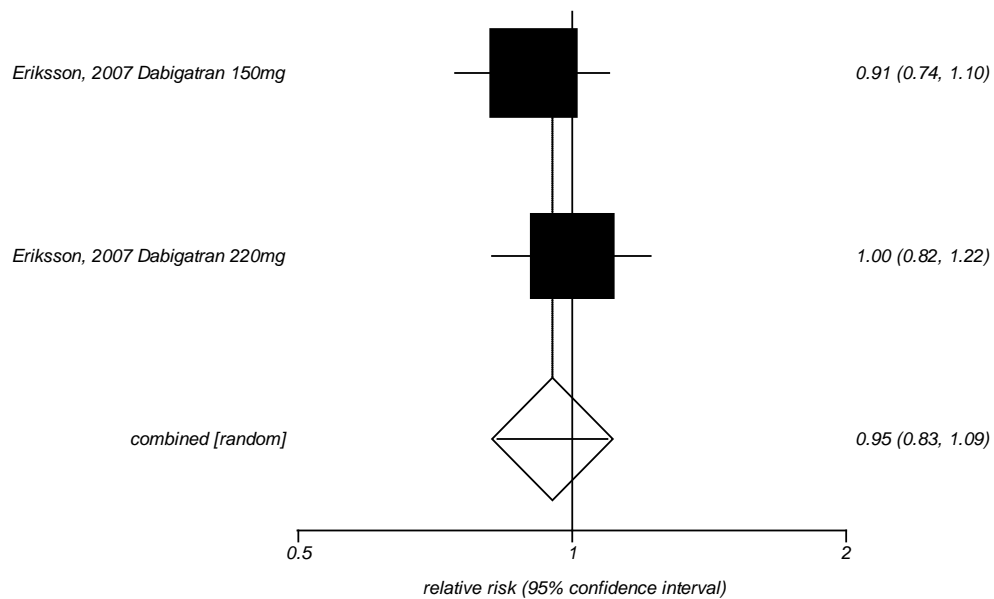


I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 126. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on asymptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement

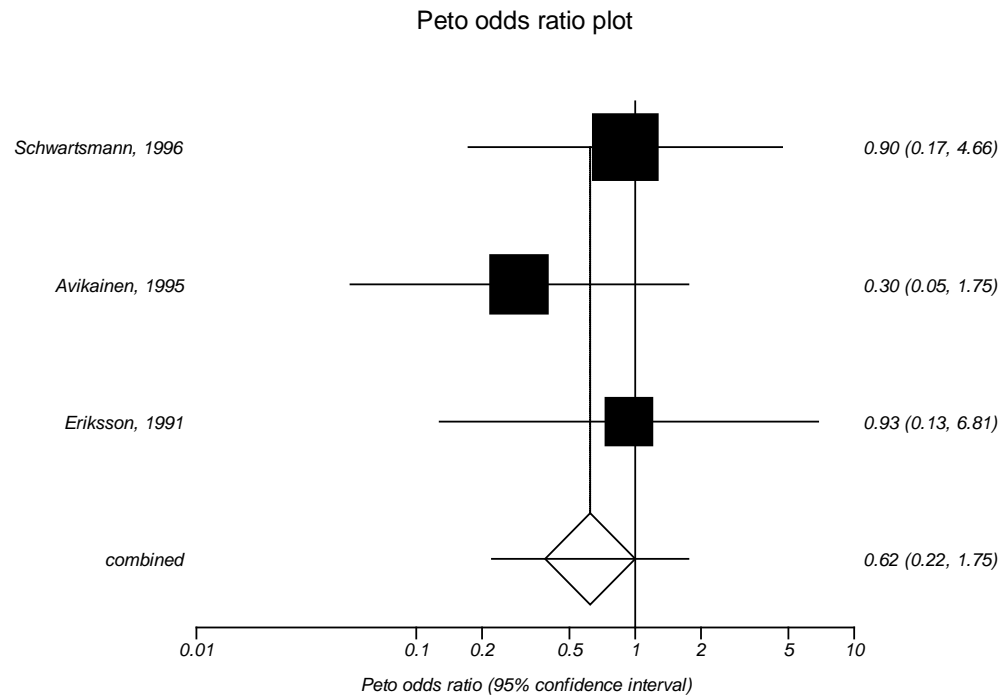
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 127. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery (same as analysis limited to total hip replacement)

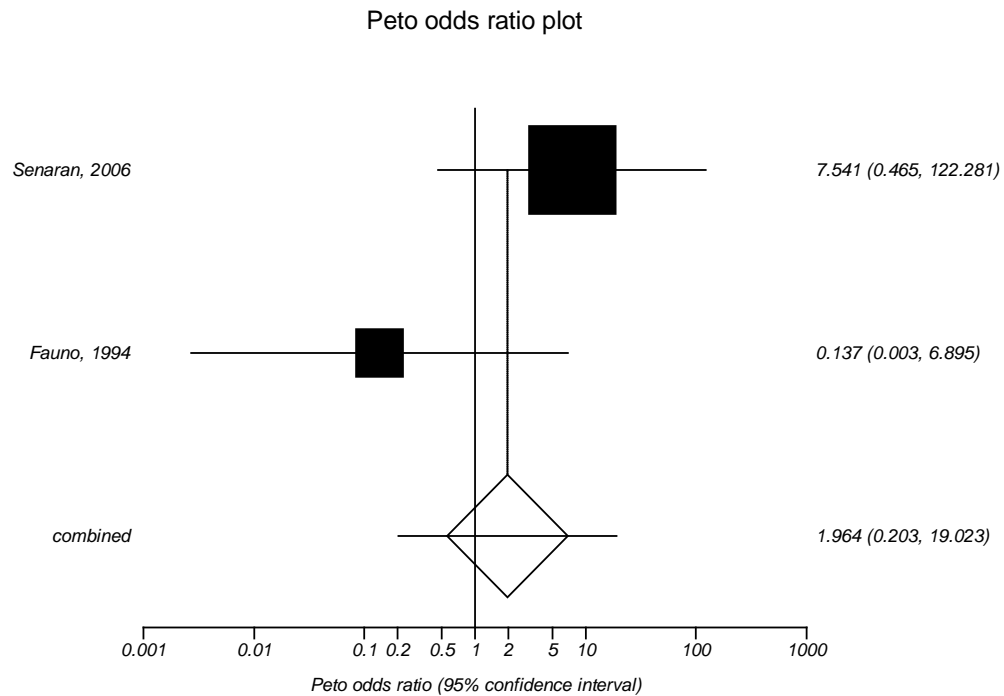


I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 128. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on symptomatic deep vein thrombosis during the postdischarge period in patients who had major orthopedic surgery

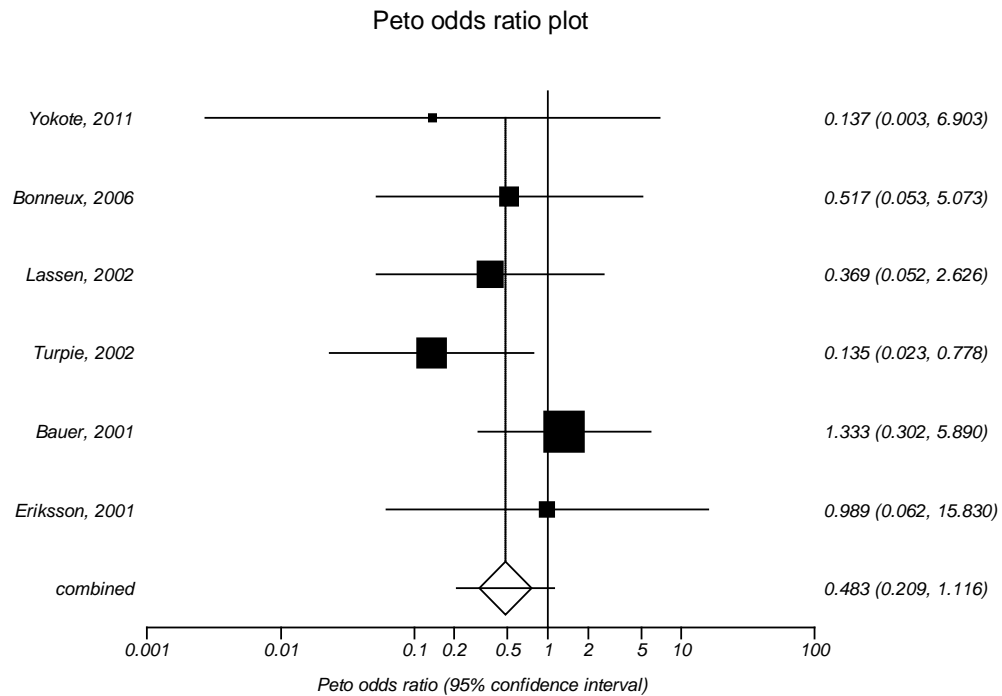


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

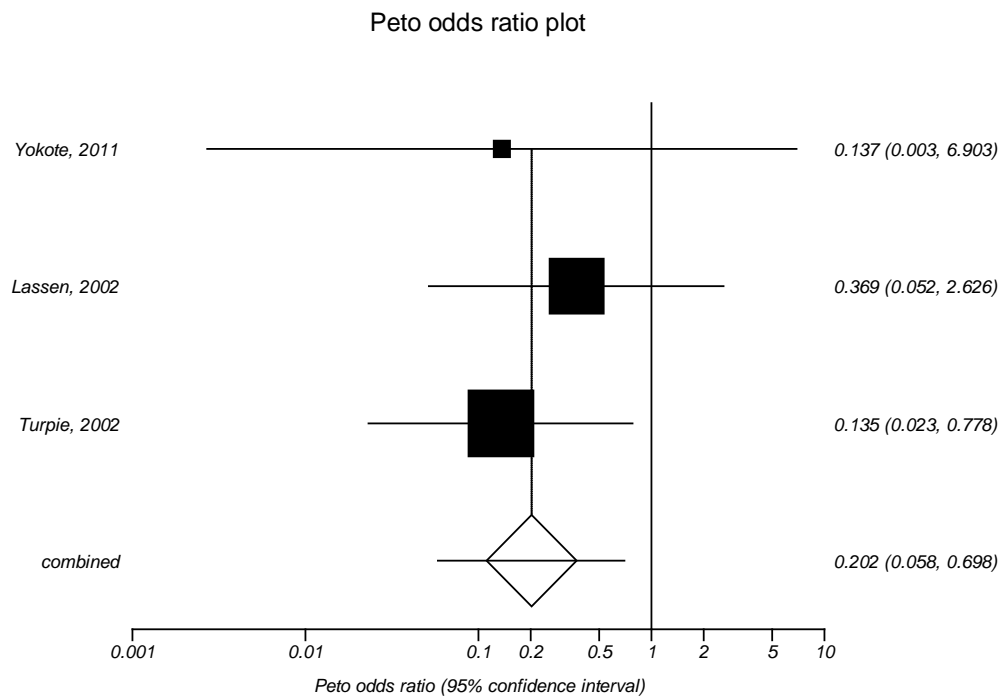
Figure 129. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)



I^2 : 0 percent
 Egger's p-value: 0.583

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

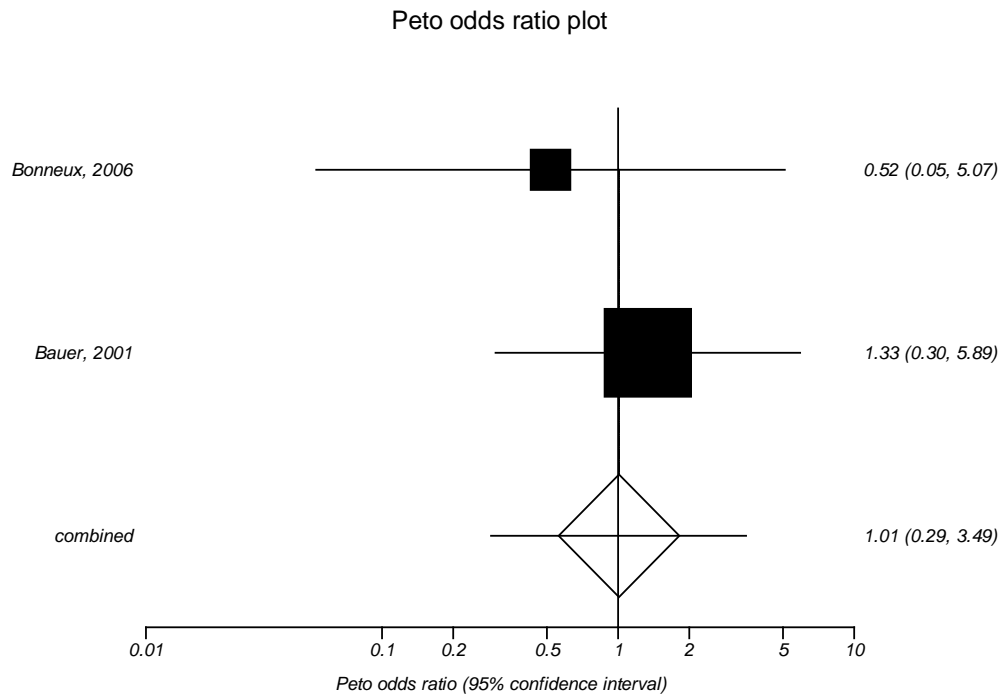
Figure 130. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

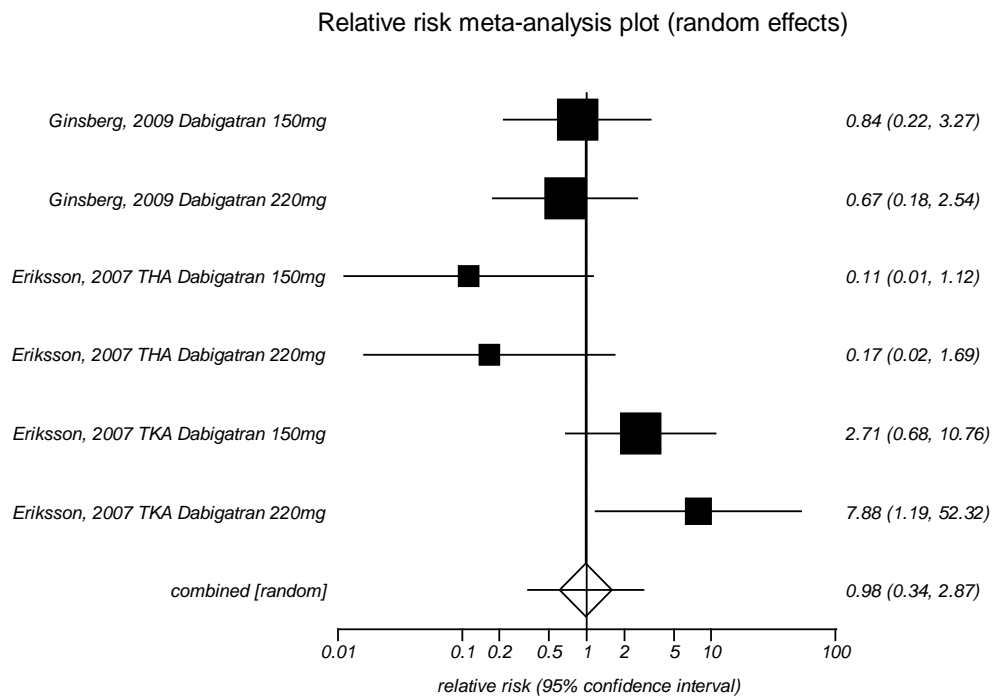
Figure 131. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 132. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)

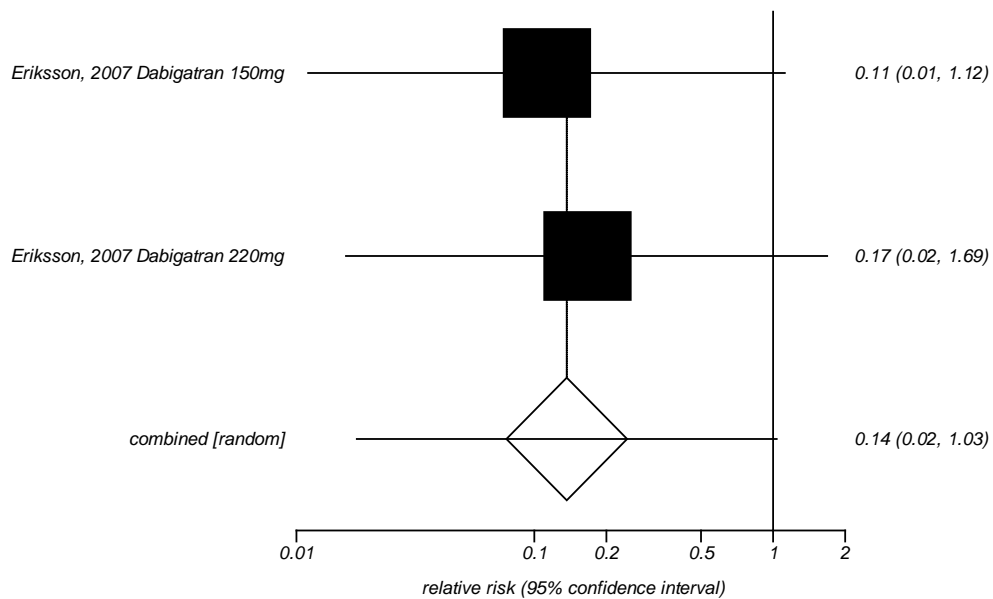


I^2 : 47.5 percent
Egger's p-value: 0.476

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 133. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery

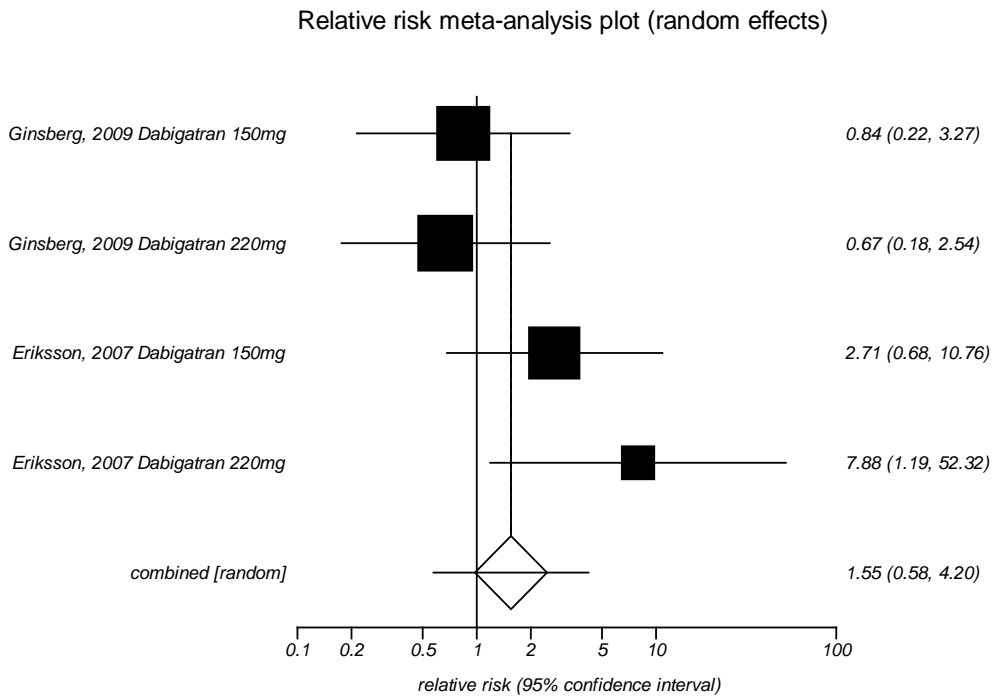
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

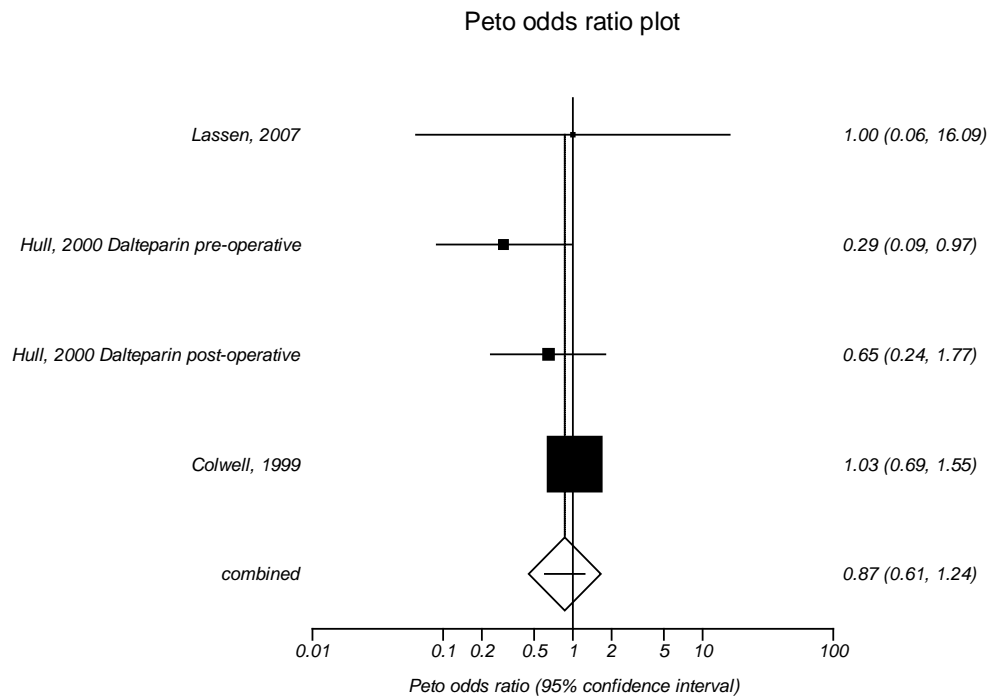
Figure 134. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 35 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

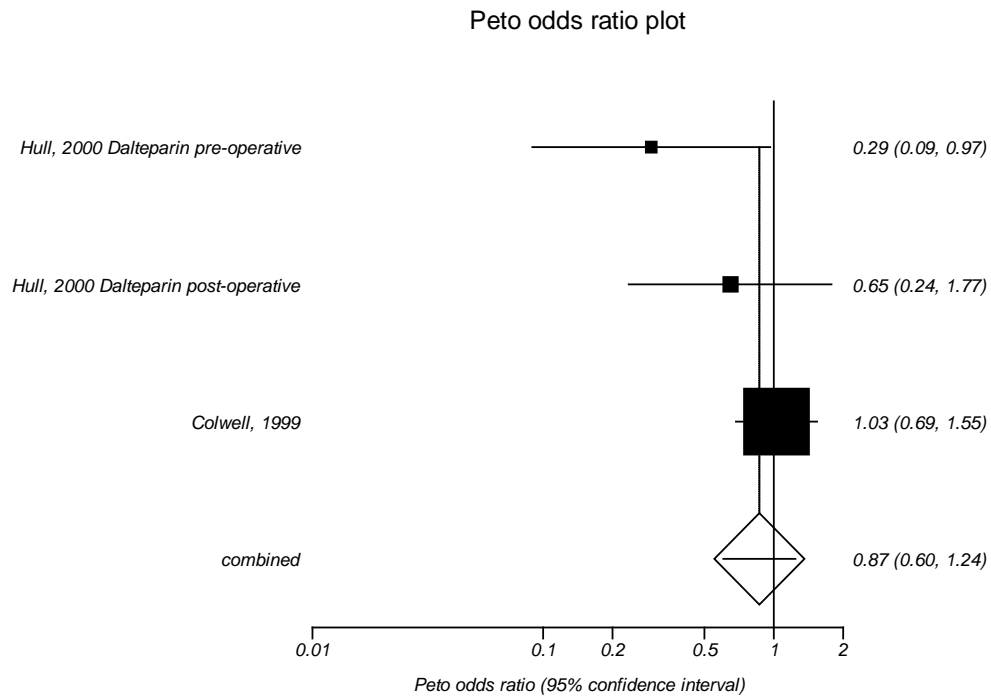
Figure 135. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery



I^2 : 28.4 percent
 Egger's p-value: 0.376

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

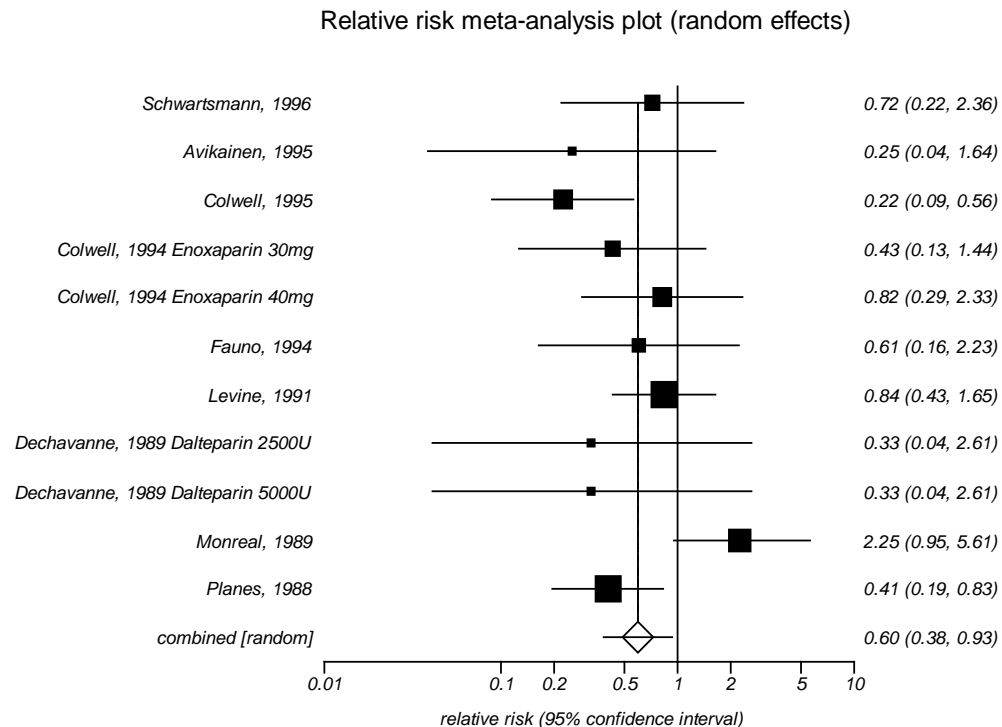
Figure 136. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on symptomatic deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 52.2 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 137. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery

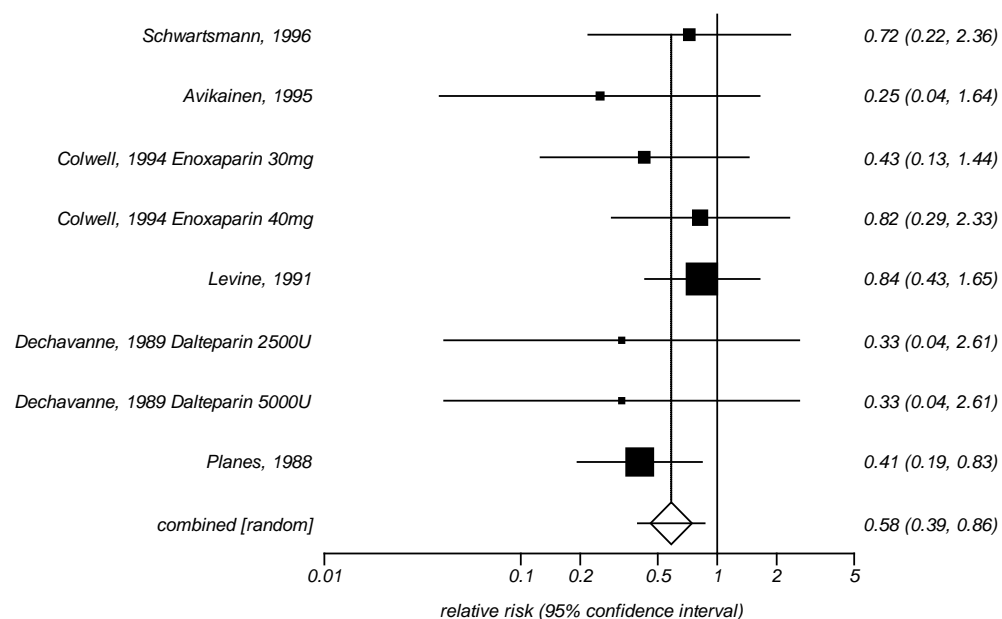


I^2 : 37 percent
 Egger's p-value: 0.450

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 138. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery

Relative risk meta-analysis plot (random effects)

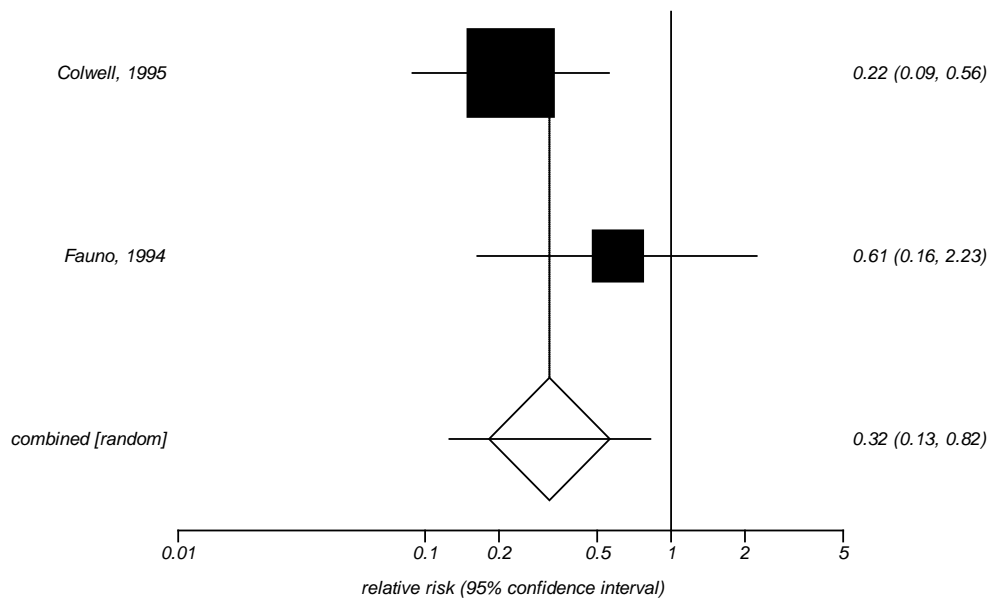


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 139. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery

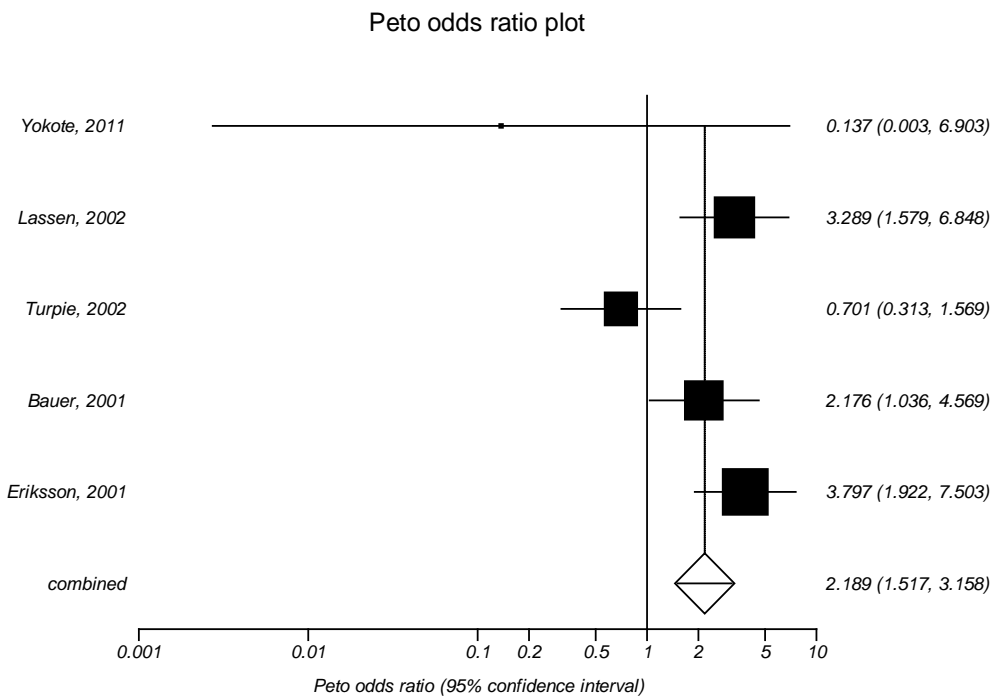
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

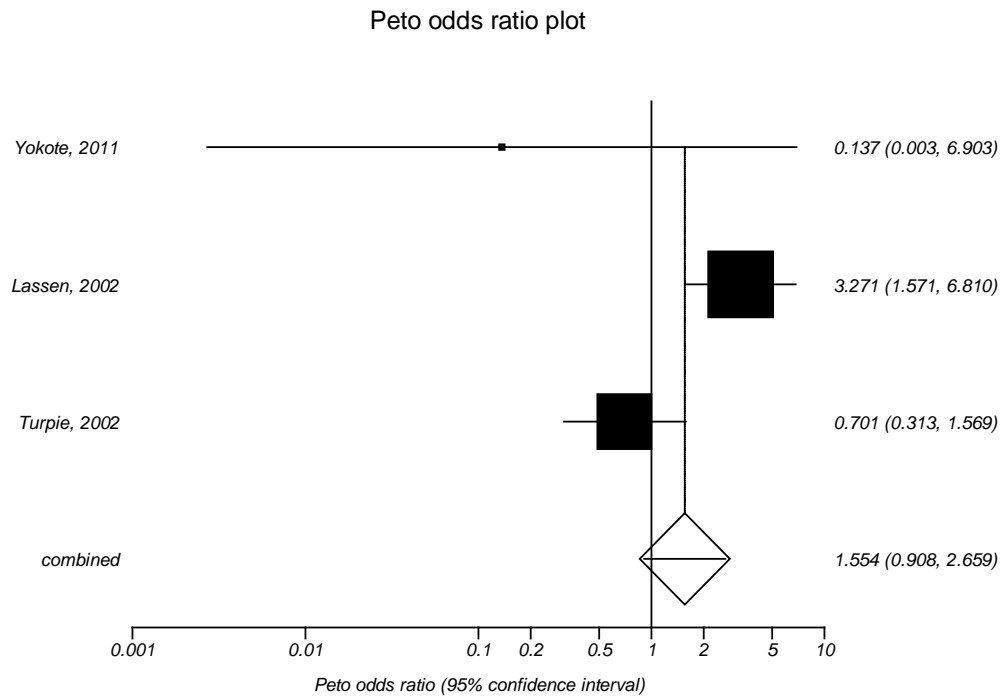
Figure 140. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery (same as 2001 to present)



I^2 : 69.9 percent
 Egger's p-value: 0.388

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

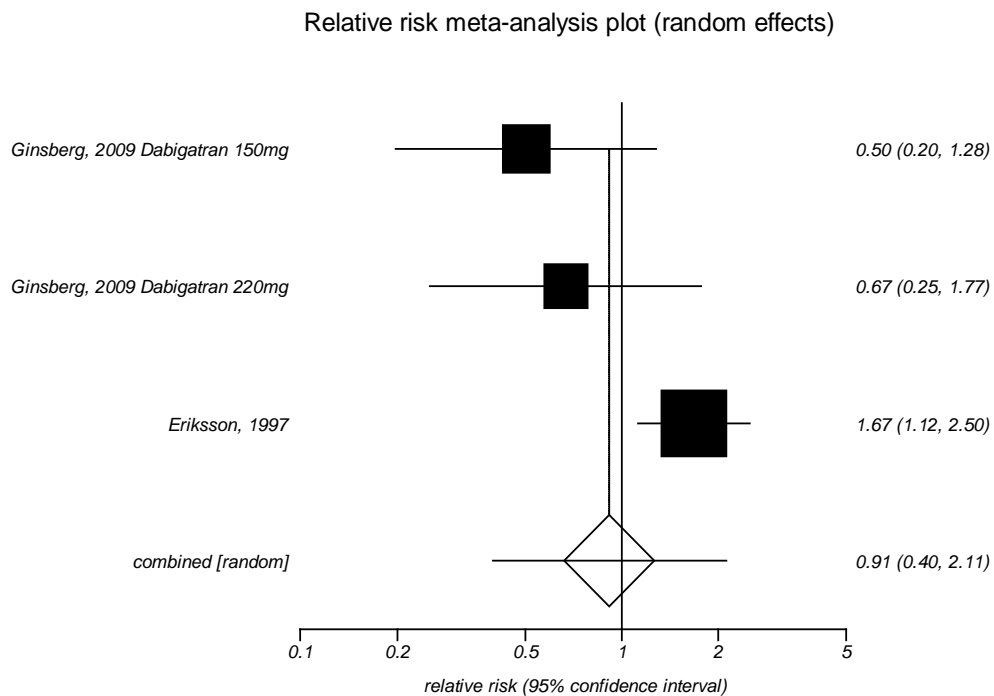
Figure 141. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 78.2 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 142. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery



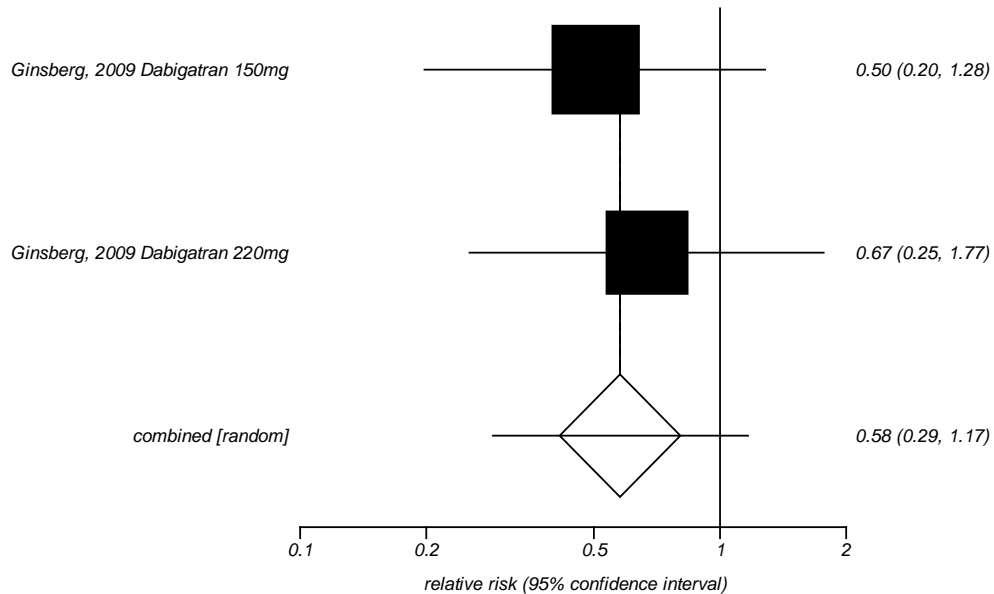
I^2 : 70.8 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 143. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to trials published from 2001 to present (same as original analysis limited to total knee replacement surgery)

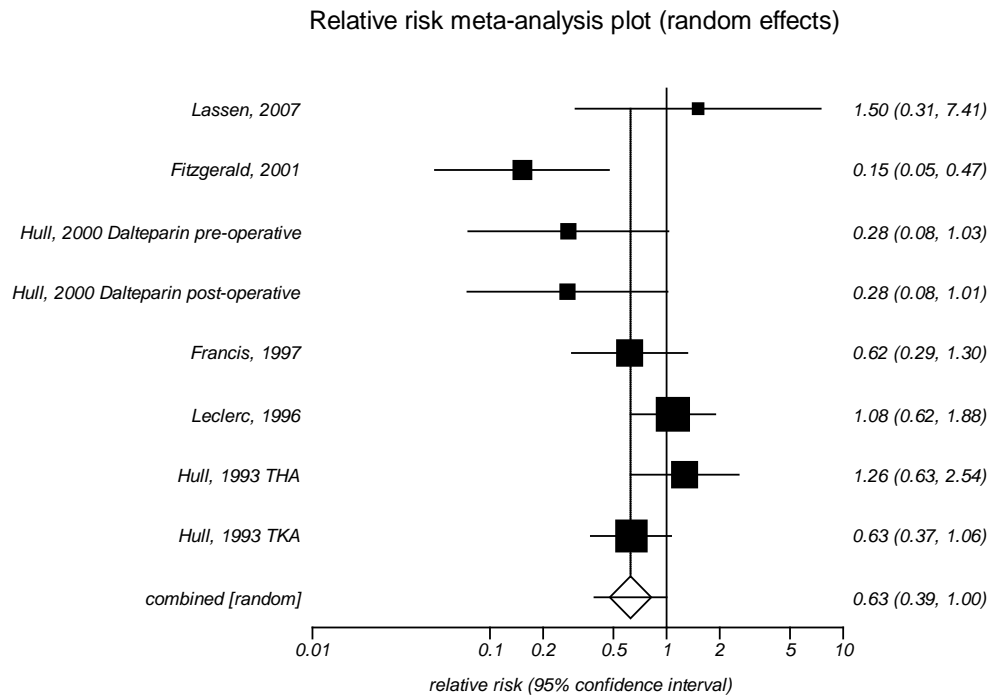
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 144. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery

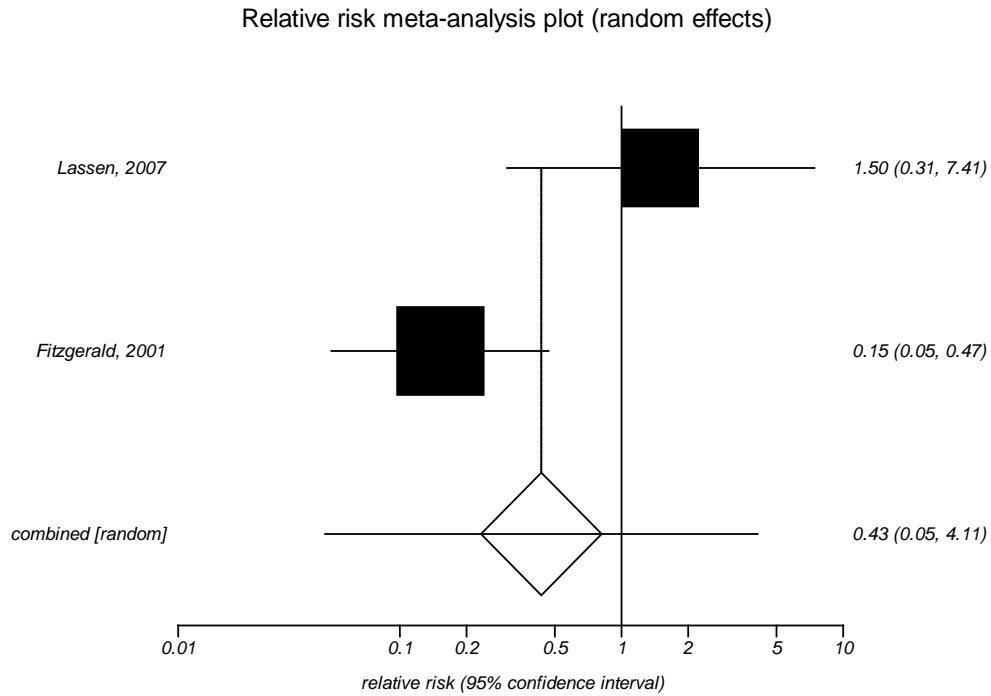


I^2 : 55.3 percent

Egger's p-value: 0.224

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

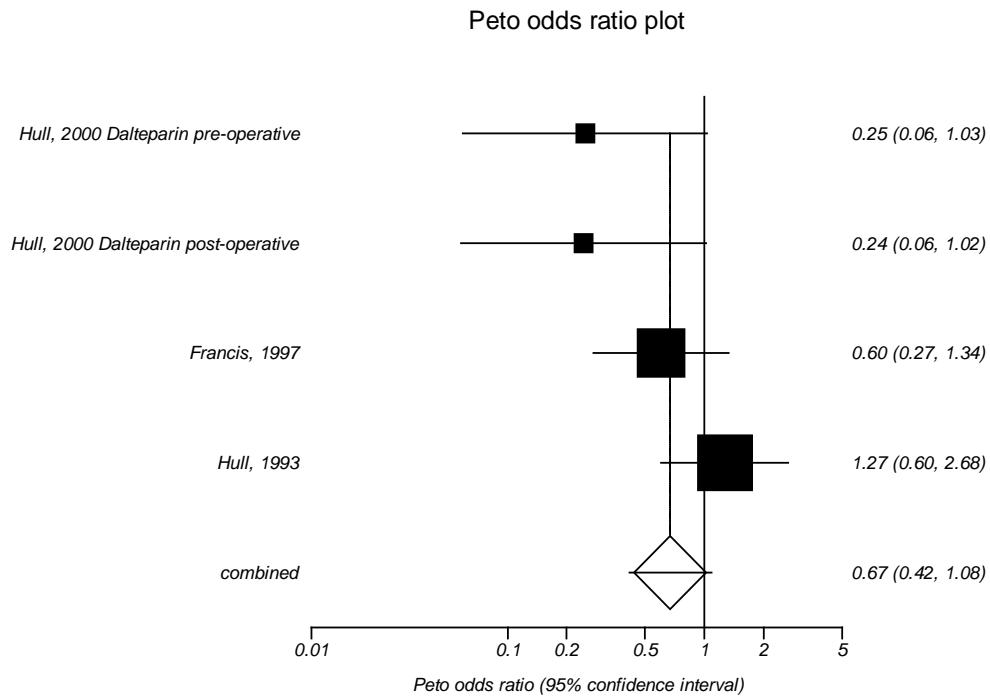
Figure 145. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to trials published from 2001 to present



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

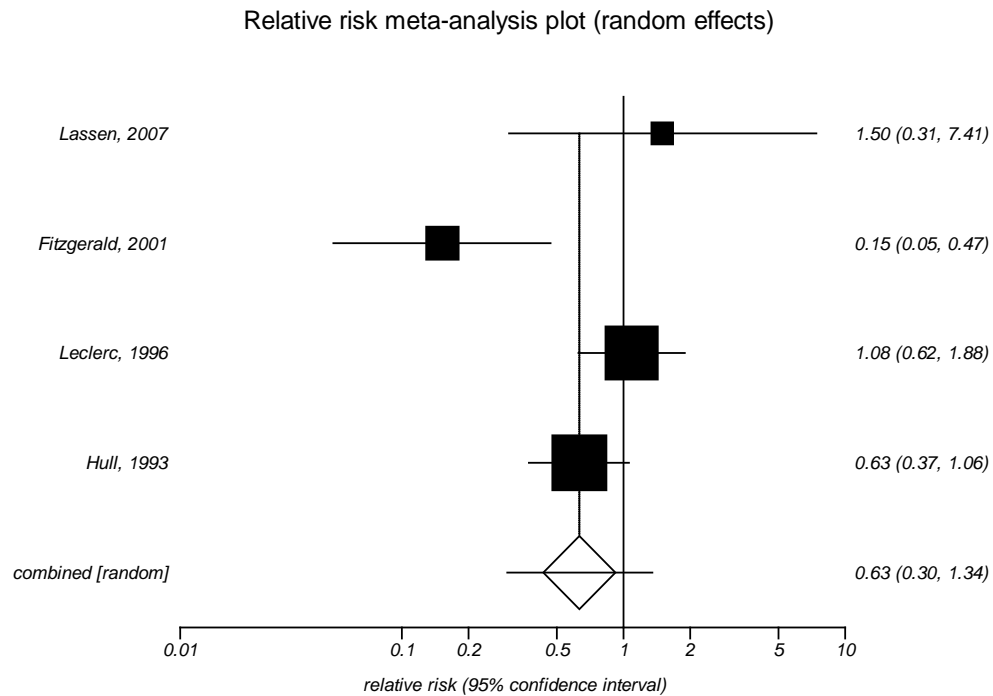
Figure 146. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 55.3 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

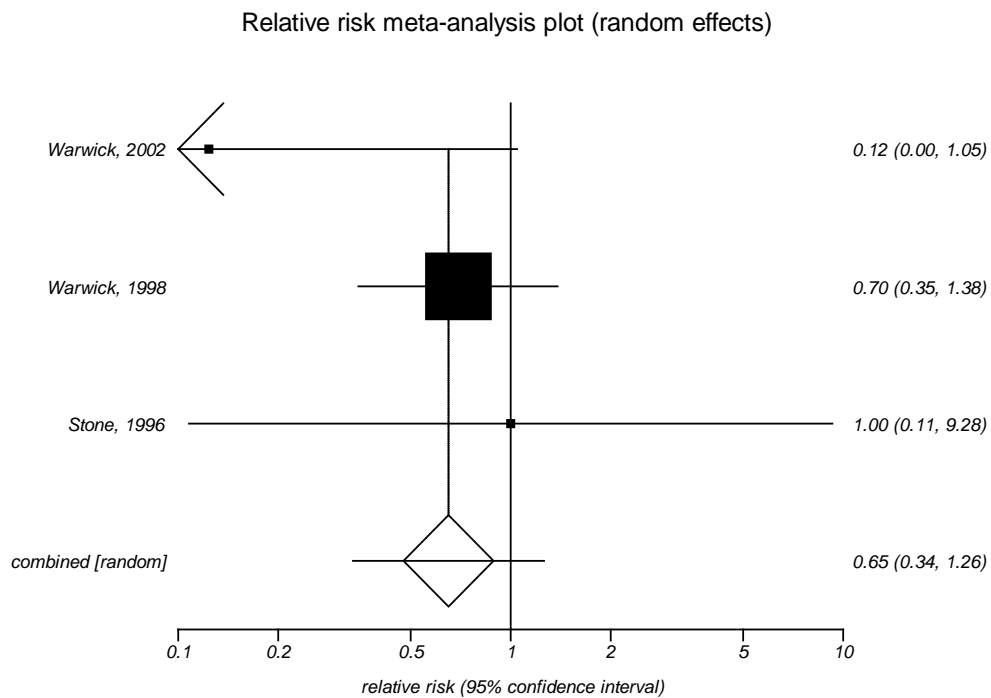
Figure 147. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 68.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 148. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery

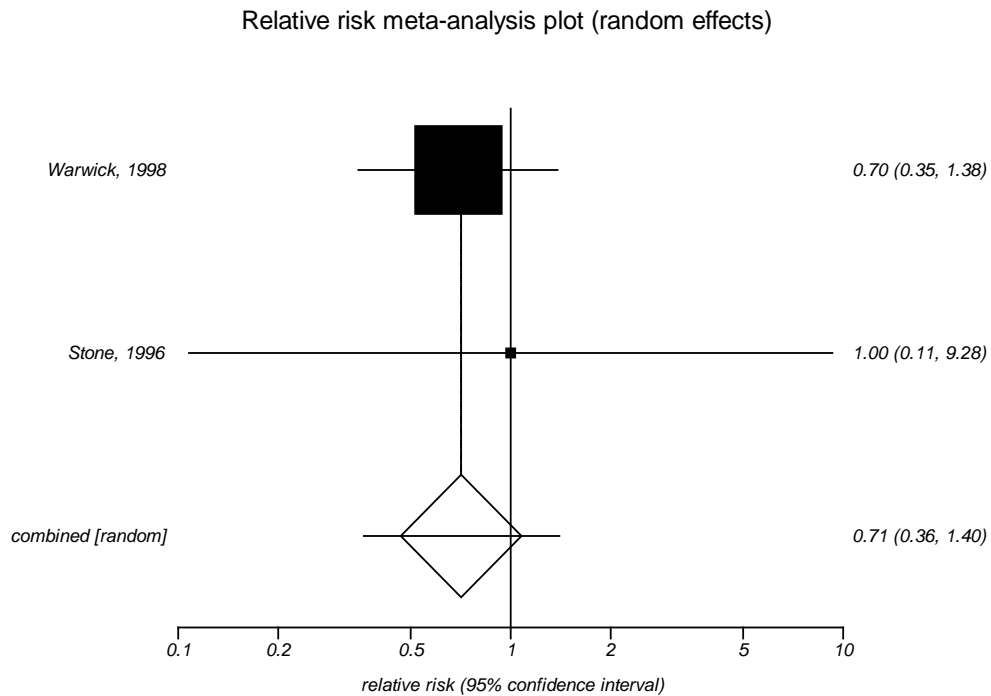


I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

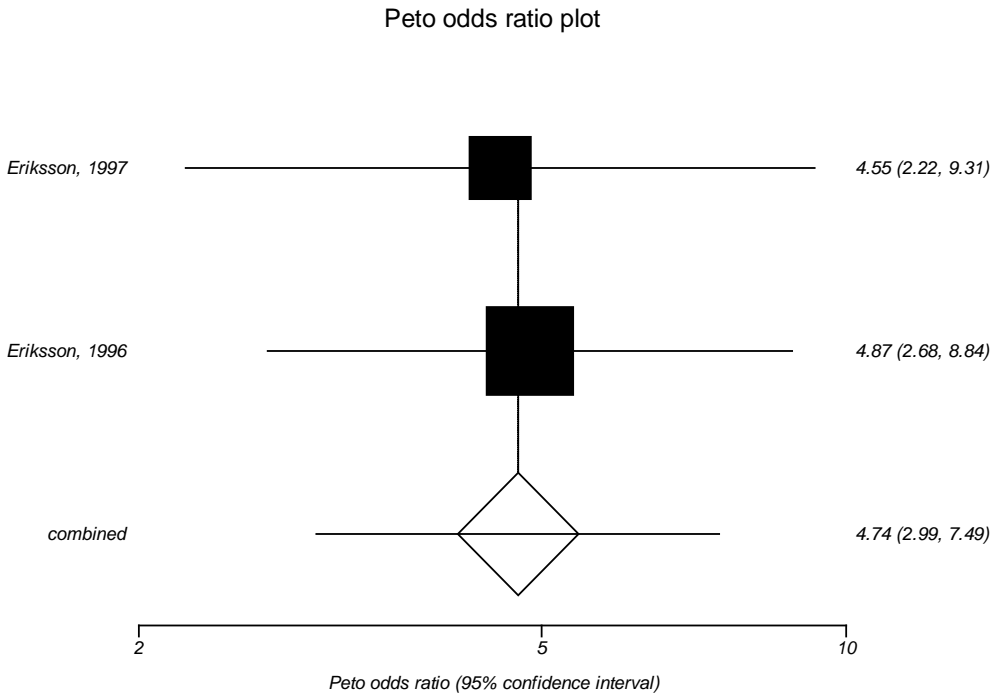
Figure 149. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 150. Impact of injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited to total hip replacement surgery)

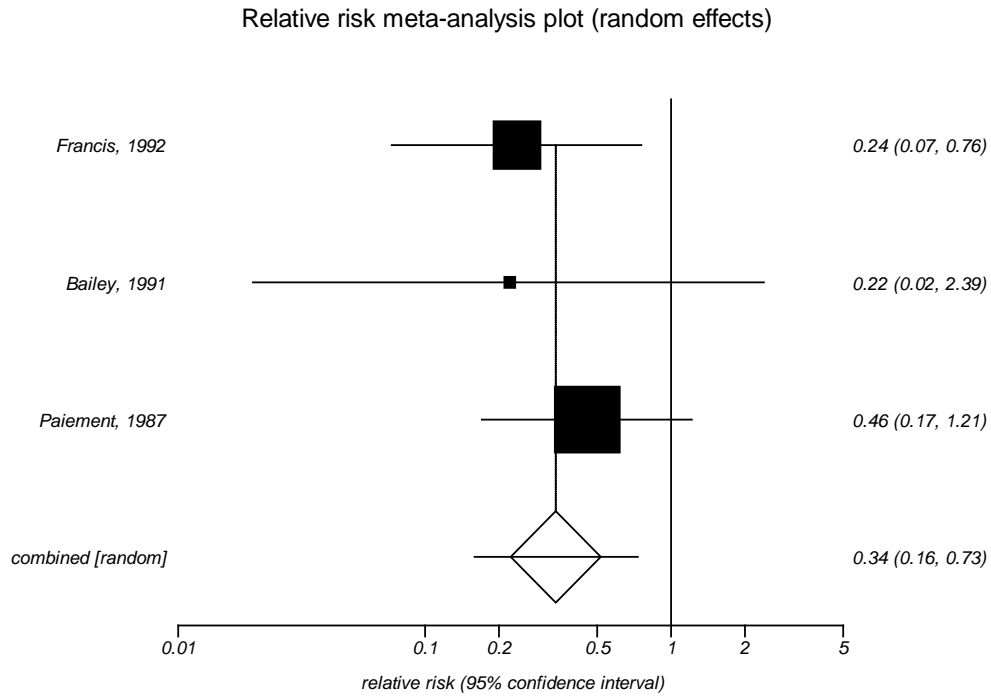


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 151. Impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on proximal deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited to total hip replacement surgery)



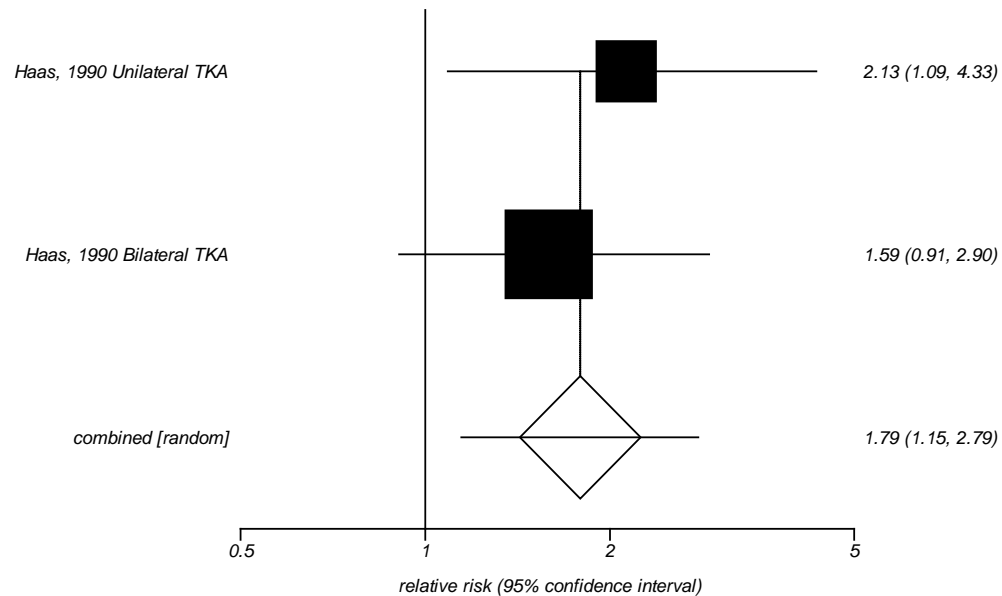
I^2 : 0 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 152. Impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery

Relative risk meta-analysis plot (random effects)

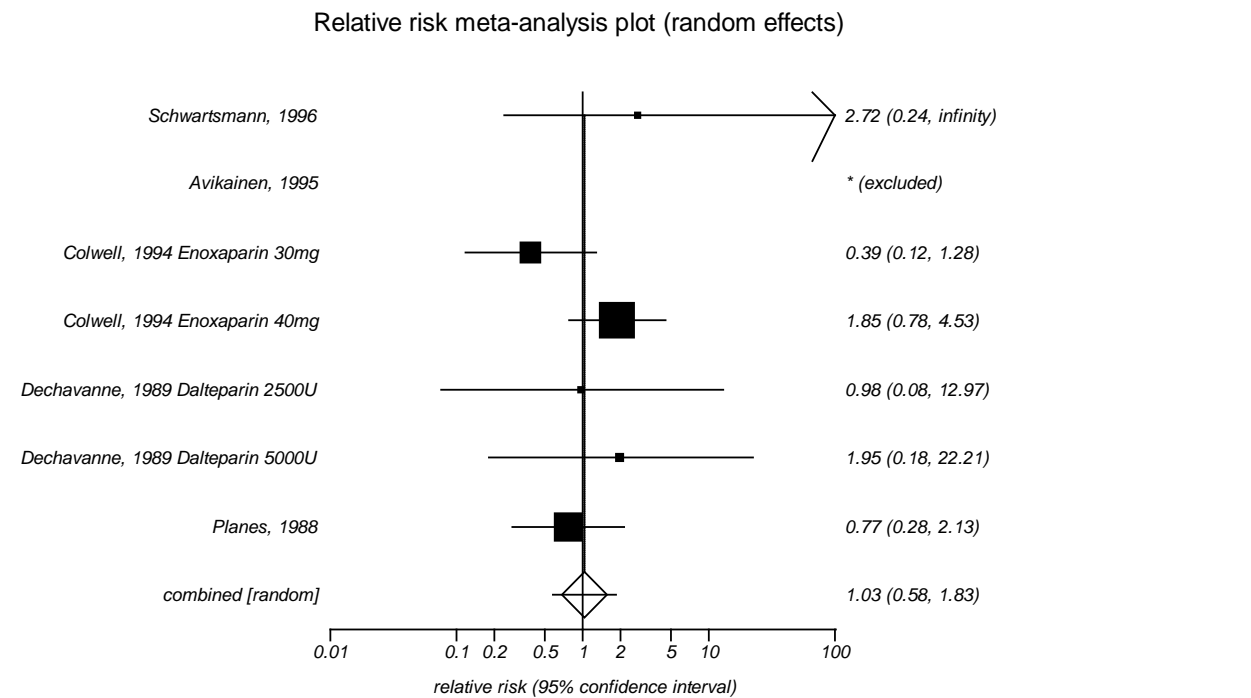


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

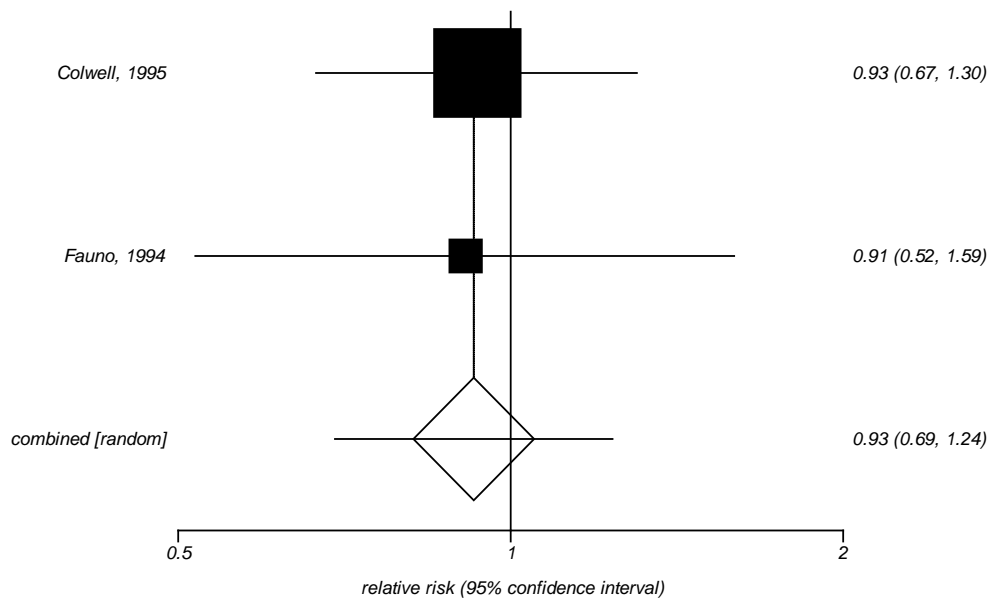
Figure 153. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 154. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total knee replacement surgery

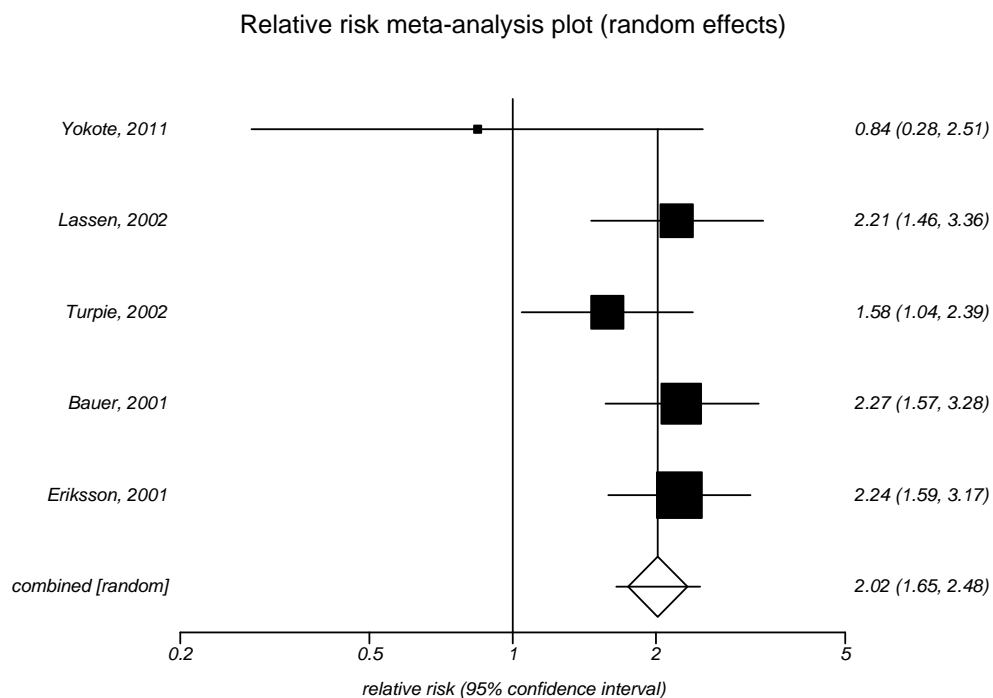
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

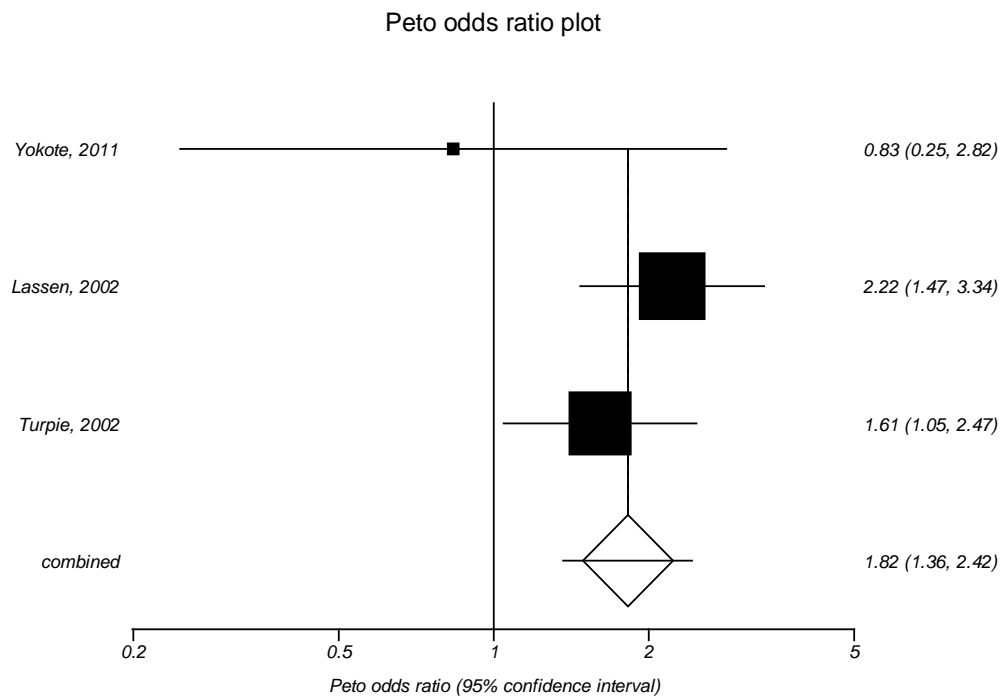
Figure 155. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited to 2001 to present)



I^2 : 10 percent
Egger's p-value: 0.106

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

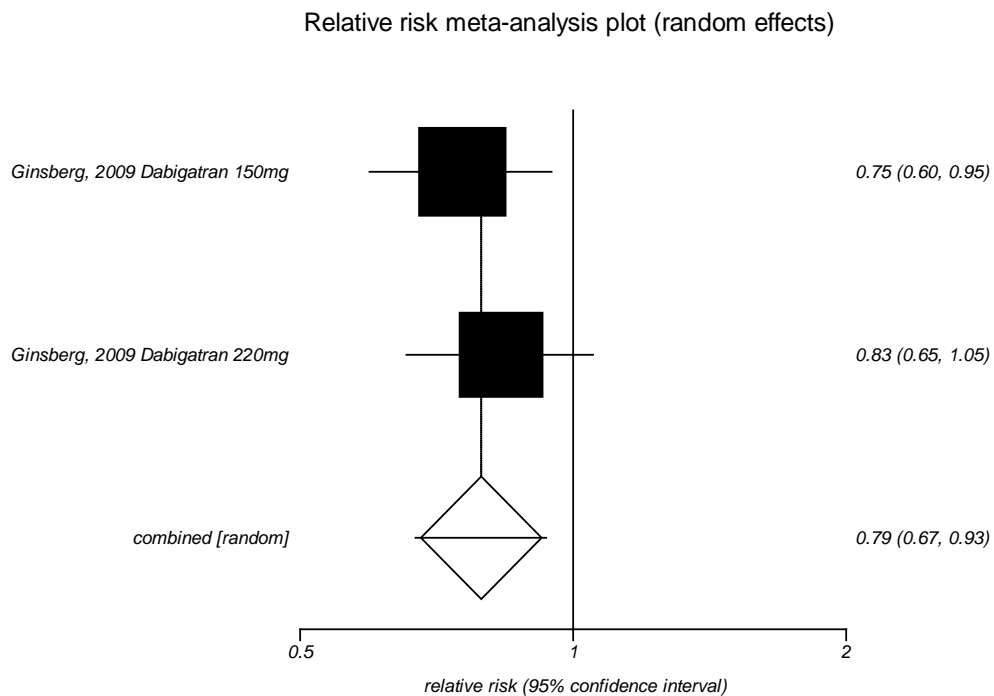
Figure 156. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 28.1 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 157. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery (same as limited to 2001 to present, same as limited to total hip replacement surgery)

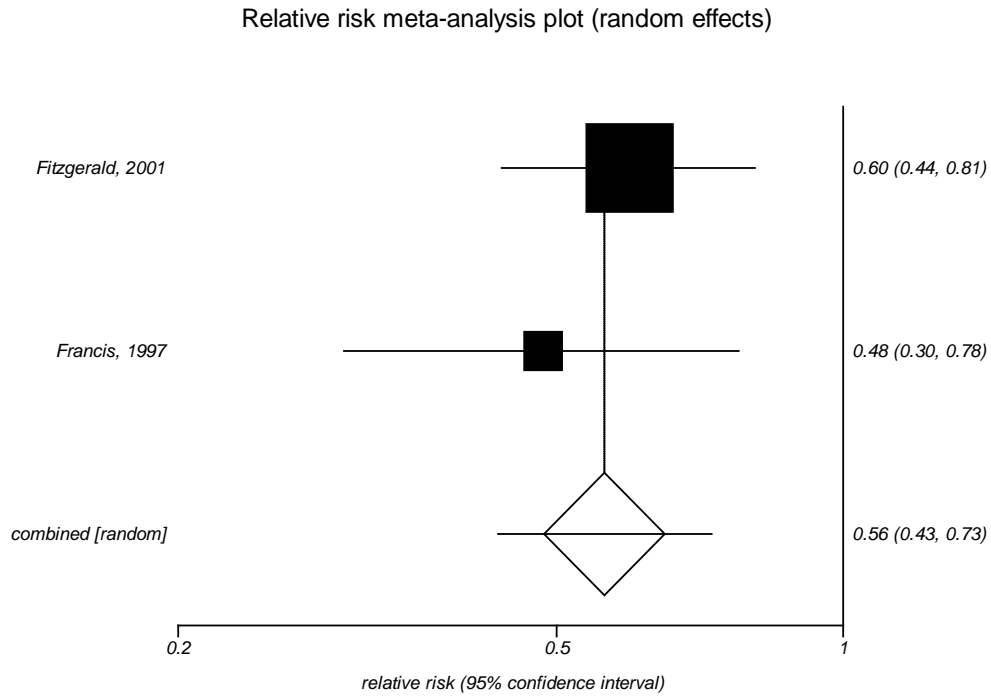


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 158. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery



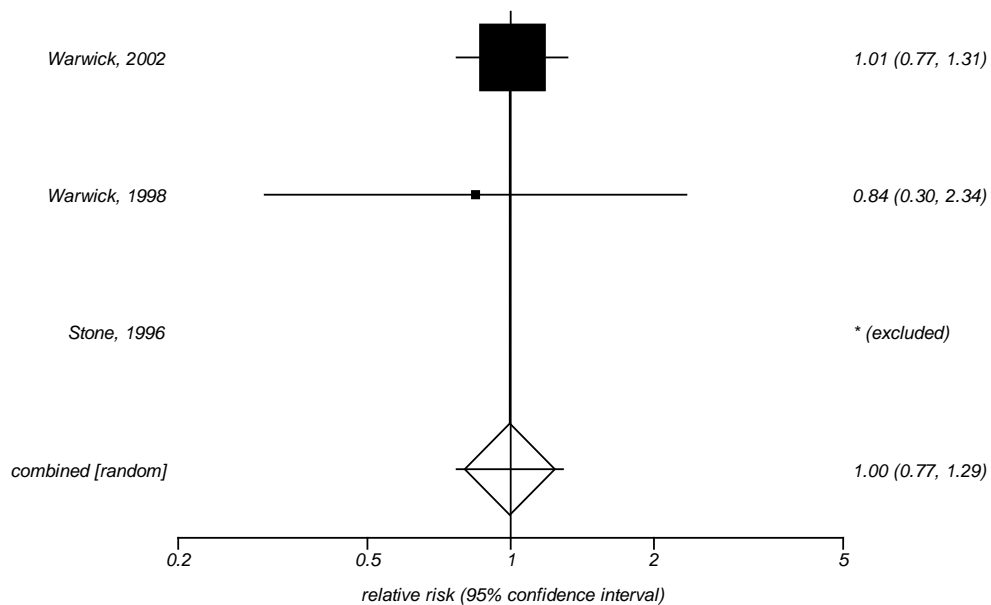
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 159. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on distal deep vein thrombosis in patients undergoing major orthopedic surgery

Relative risk meta-analysis plot (random effects)

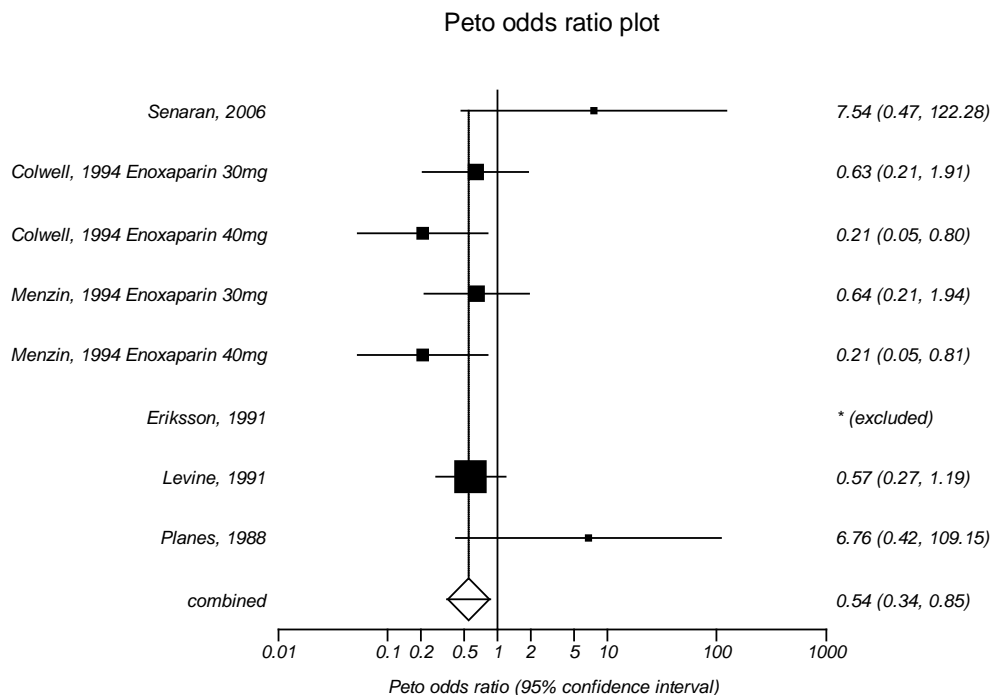


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

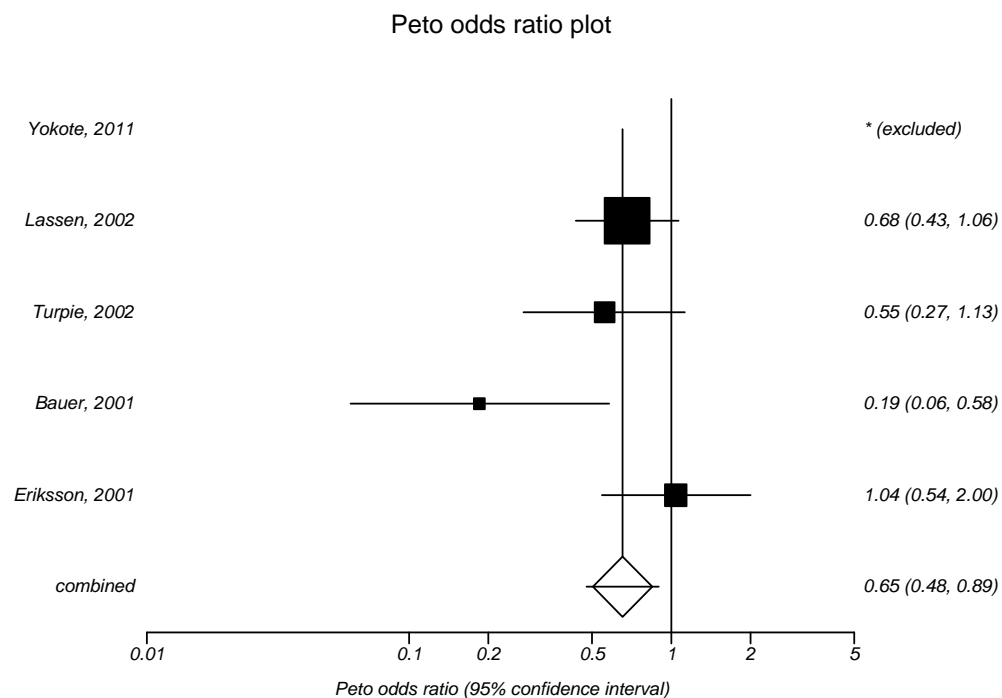
Figure 160. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on major bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 43.5 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

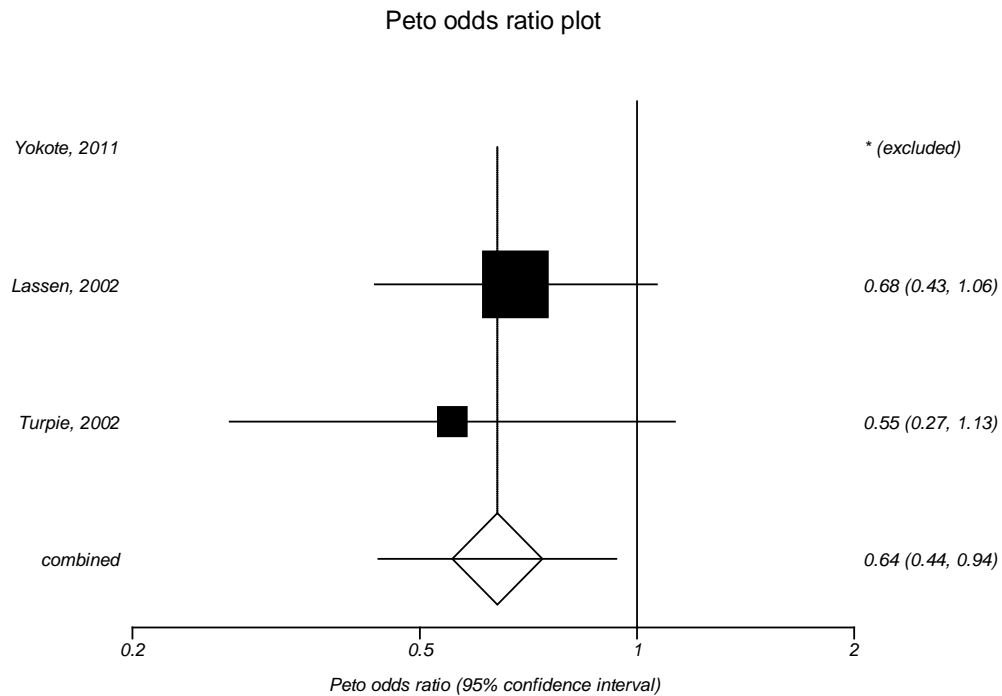
Figure 161. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on major bleeding in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001 to the present)



I^2 : 56.6 percent
 Egger's p-value: 0.347

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 162. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors on major bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery

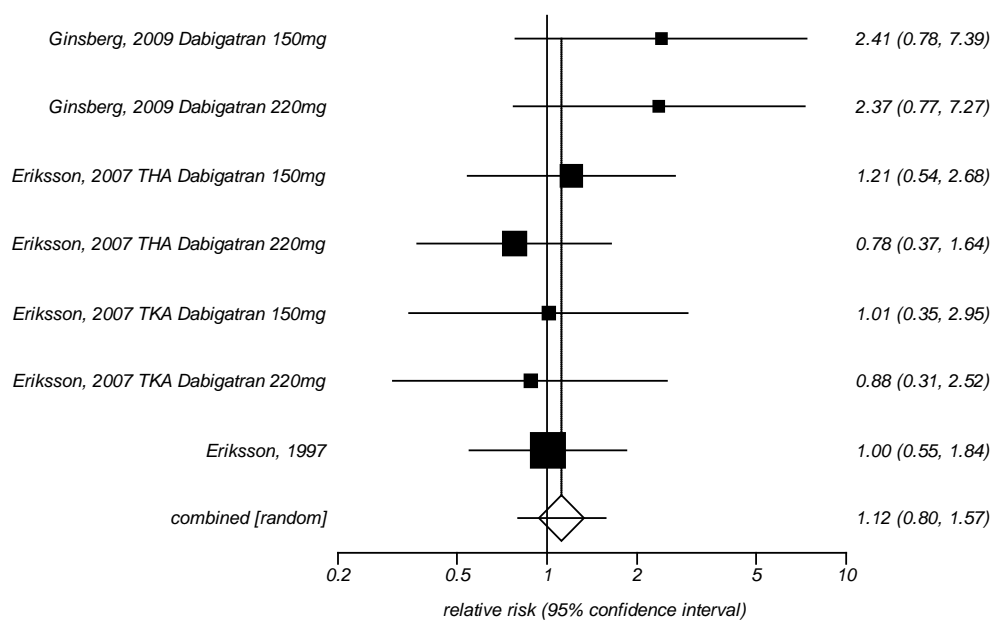


I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 163. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on major bleeding in patients undergoing major orthopedic surgery

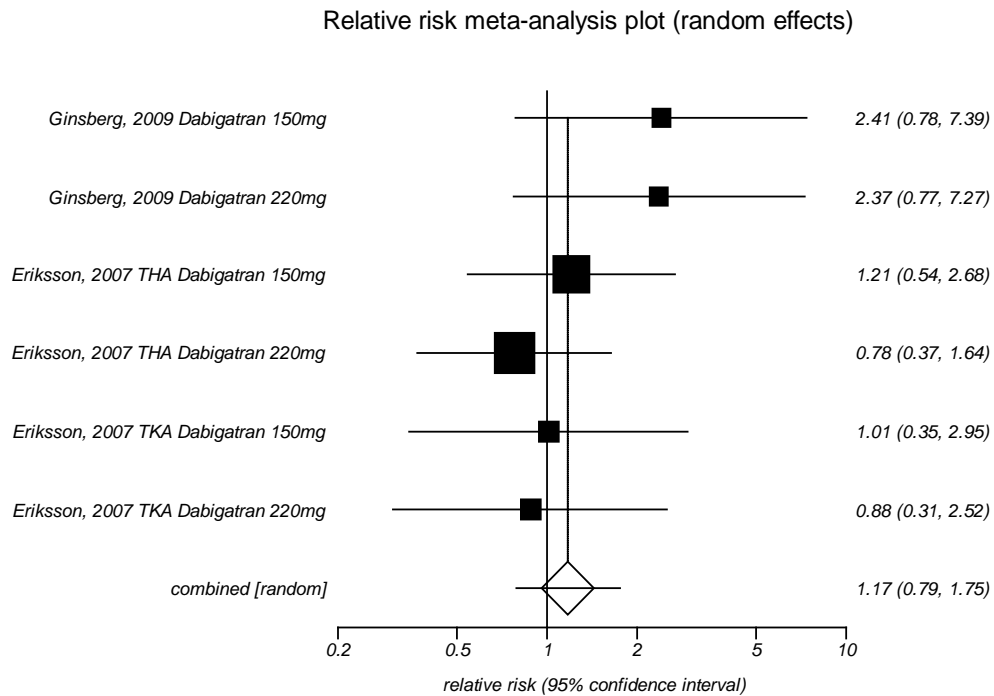
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent
 Egger's p-value: 0.175

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

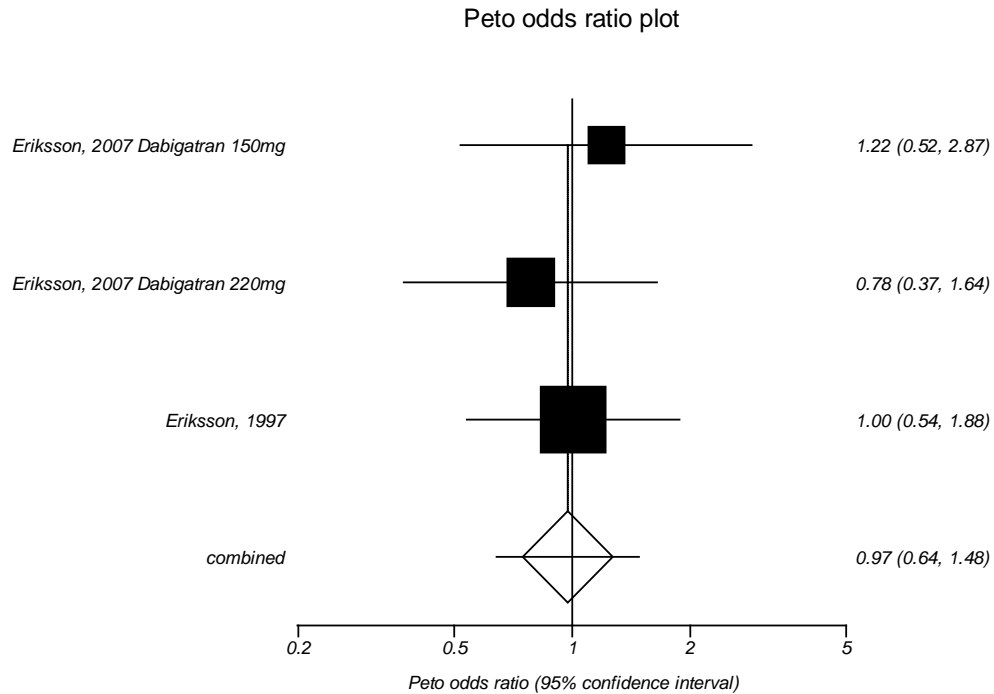
Figure 164. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on major bleeding in patients undergoing major orthopedic surgery limited to trials published from 2001 to the present



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

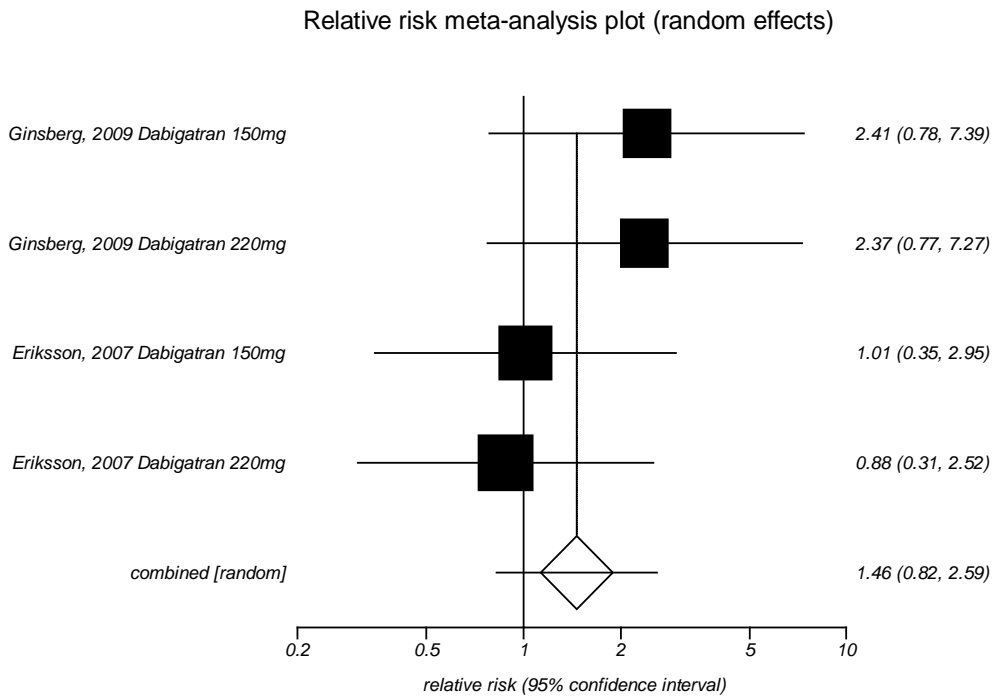
Figure 165. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on major bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

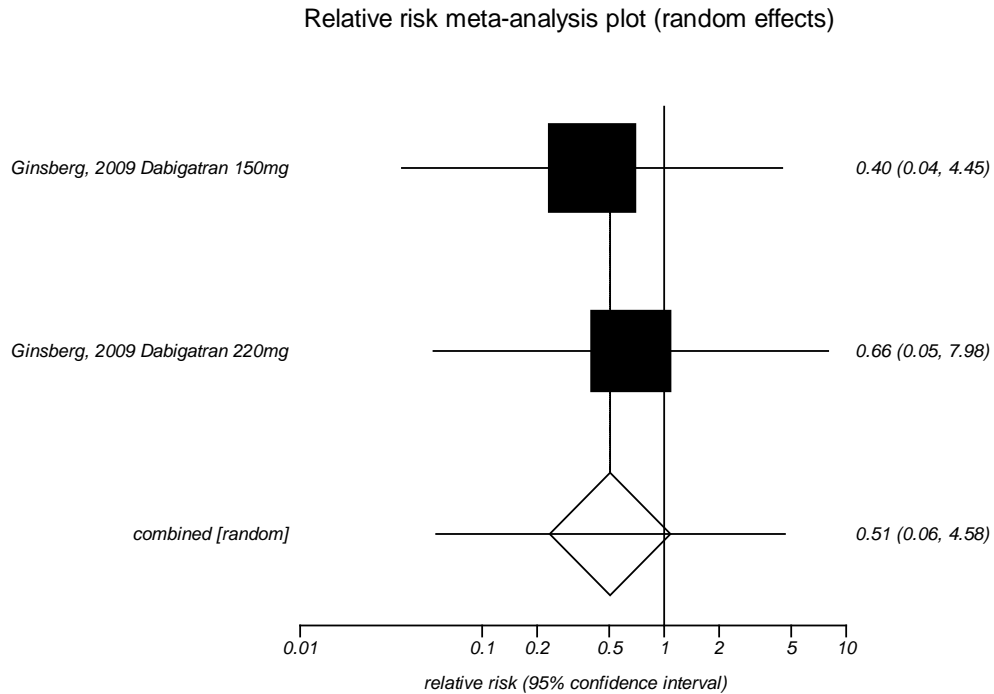
Figure 166. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on major bleeding in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 167. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on major bleeding during the postdischarge period in patients who had total knee replacement surgery



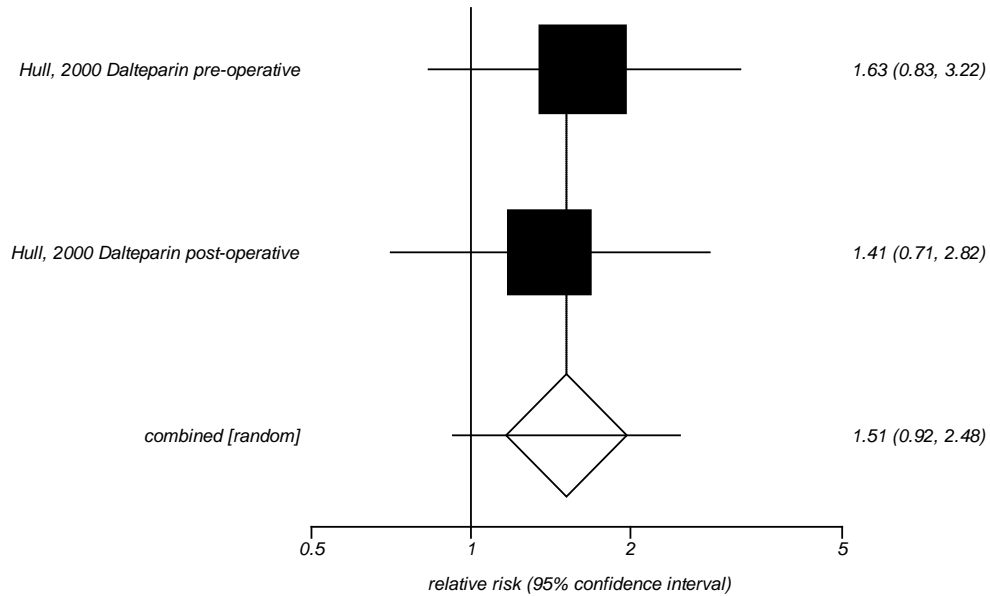
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 168. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major bleeding during days 0 to 1 in patients who had total hip replacement surgery

Relative risk meta-analysis plot (random effects)



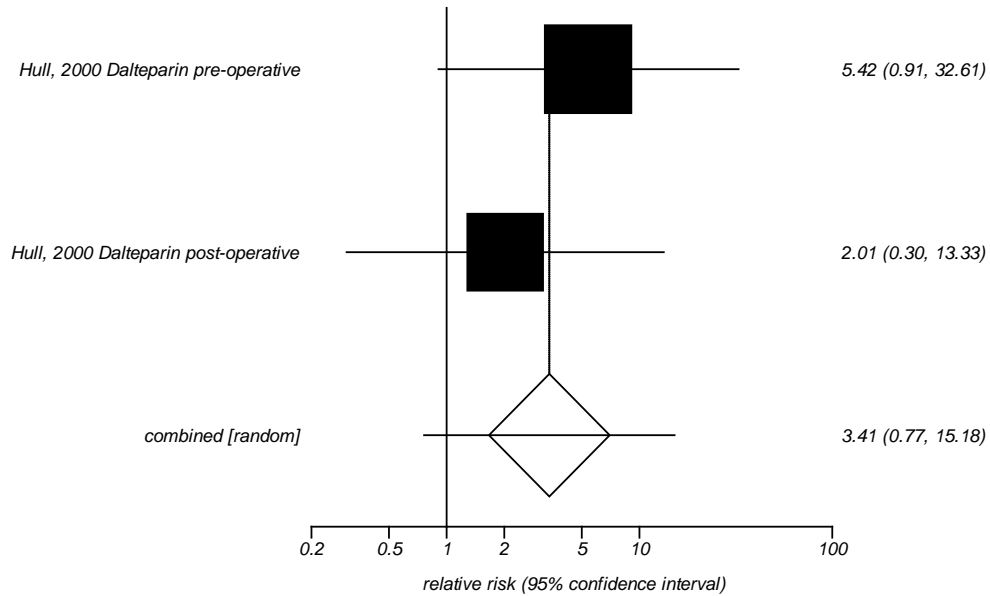
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 169. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major bleeding during days 2 to 8 in patients who had total hip replacement surgery

Relative risk meta-analysis plot (random effects)

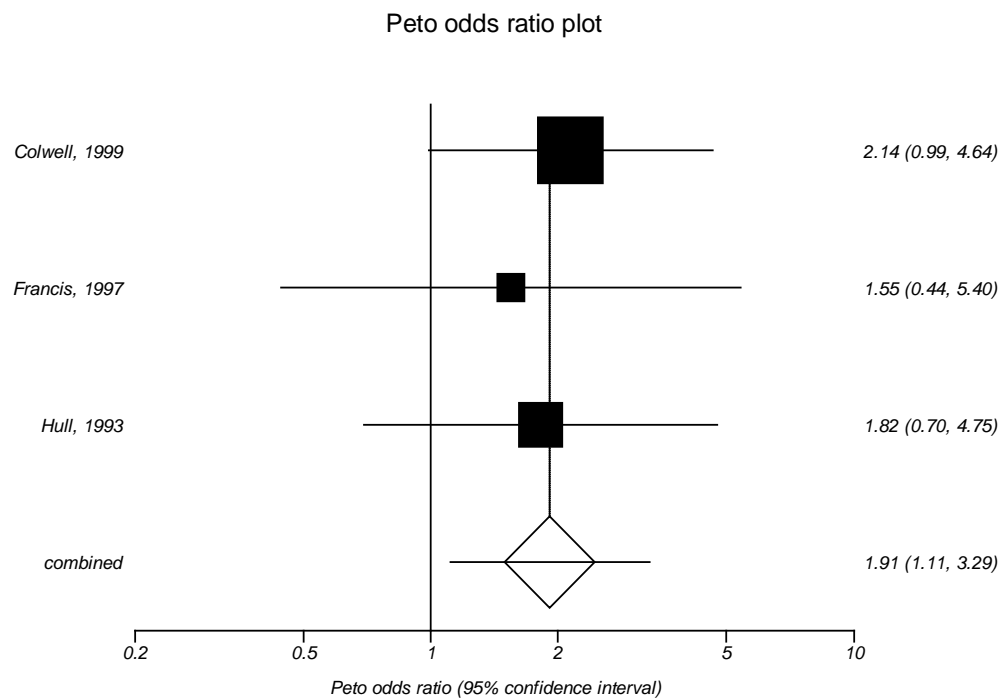


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

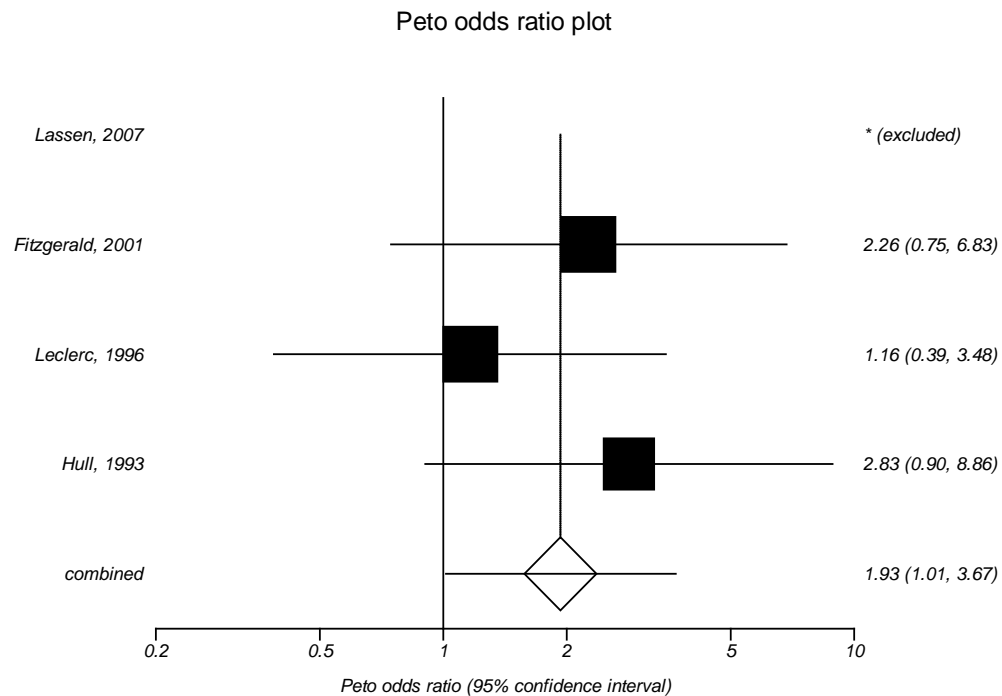
Figure 170. Impact of injectable low molecular weight heparin versus oral vitamin k antagonists on major bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

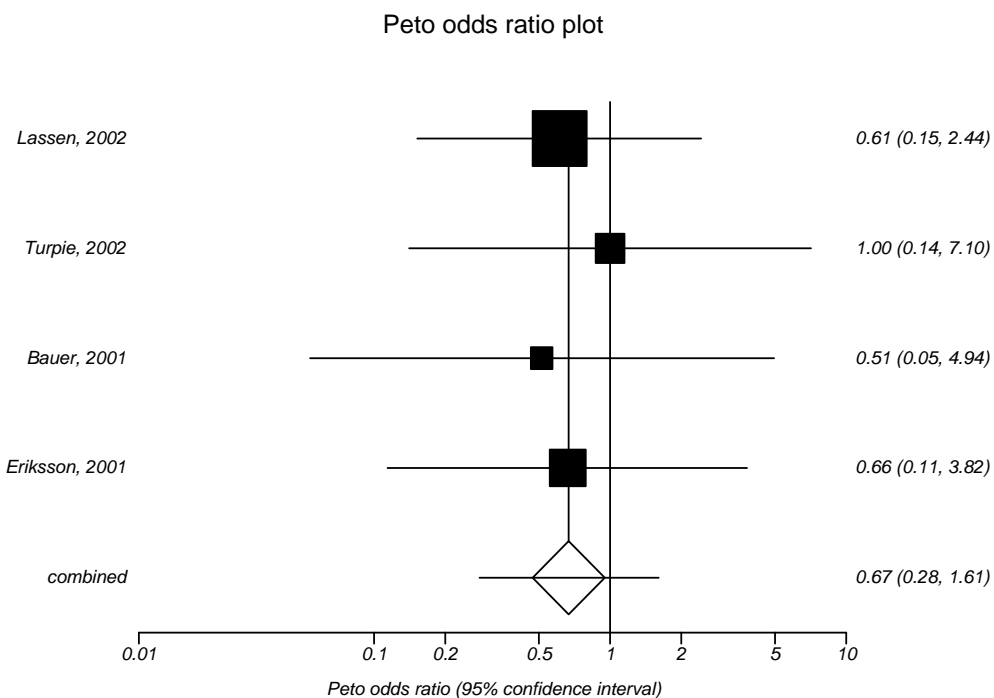
Figure 171. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major bleeding in patients undergoing major orthopedic surgery limited to total knee replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

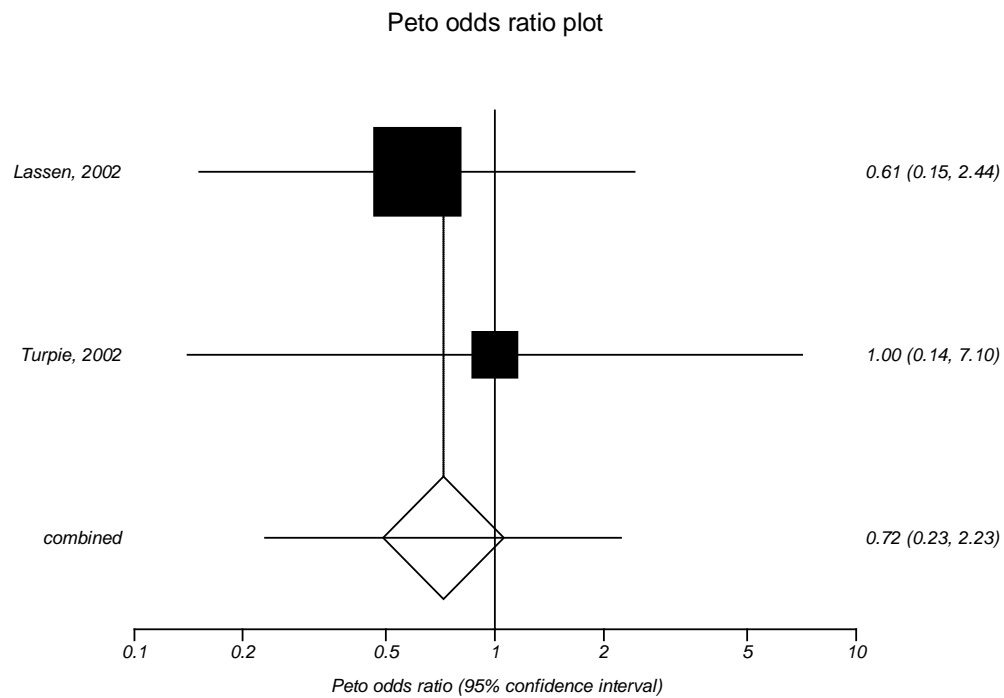
Figure 172. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa antagonists on major bleeding leading to reoperation (same as analysis limited to trials published from 2001-present)



I^2 : 0 percent
 Egger's p-value: 0.855

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

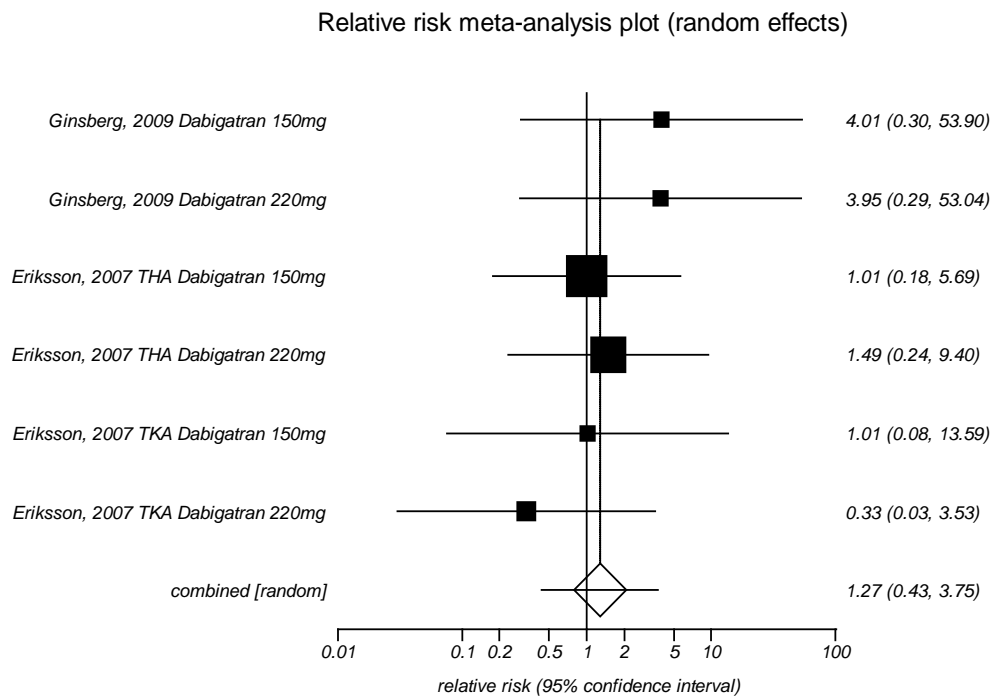
Figure 173. Impact of injectable low molecular weight heparin versus injectable or oral factor Xa antagonists on major bleeding leading to reoperation in patients undergoing major orthopedic surgery limited to total hip replacement



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 174. Impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on major bleeding leading to reoperation in patients who had major orthopedic surgery (same as analysis limited to trials published from 2001-present)



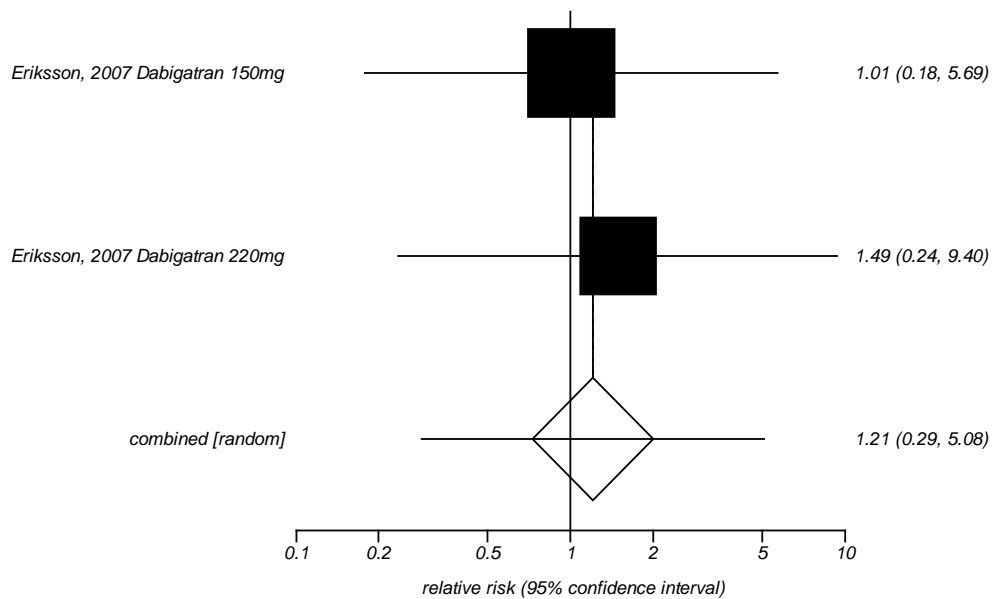
I^2 : 0 percent

Egger's p-value: 0.614

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 175. Impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on major bleeding leading to reoperation in patients who had major orthopedic surgery limited to total hip replacement surgery

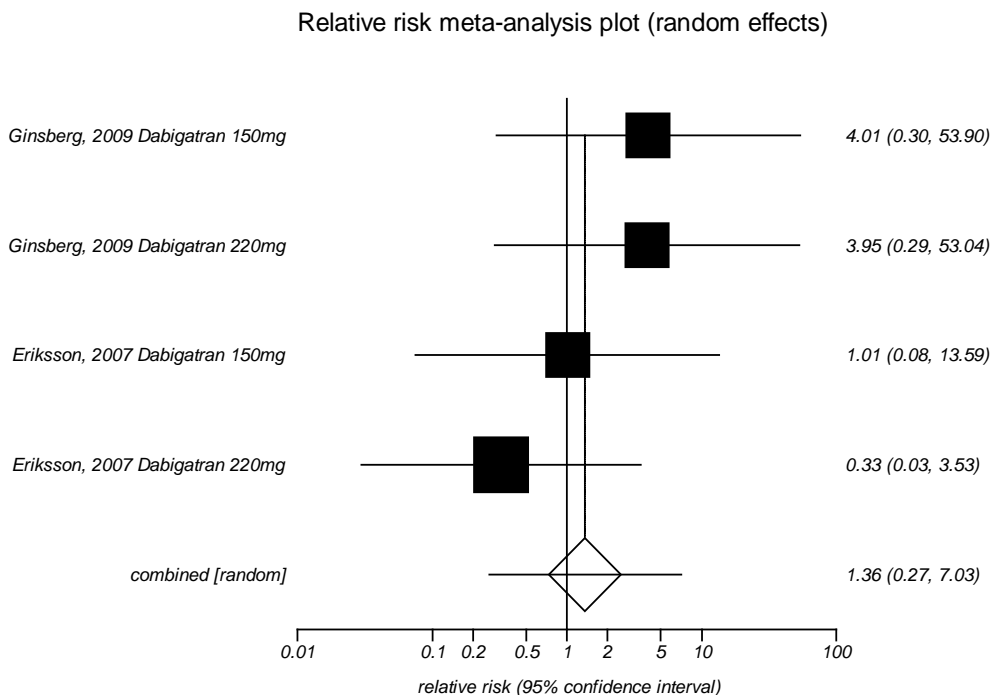
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

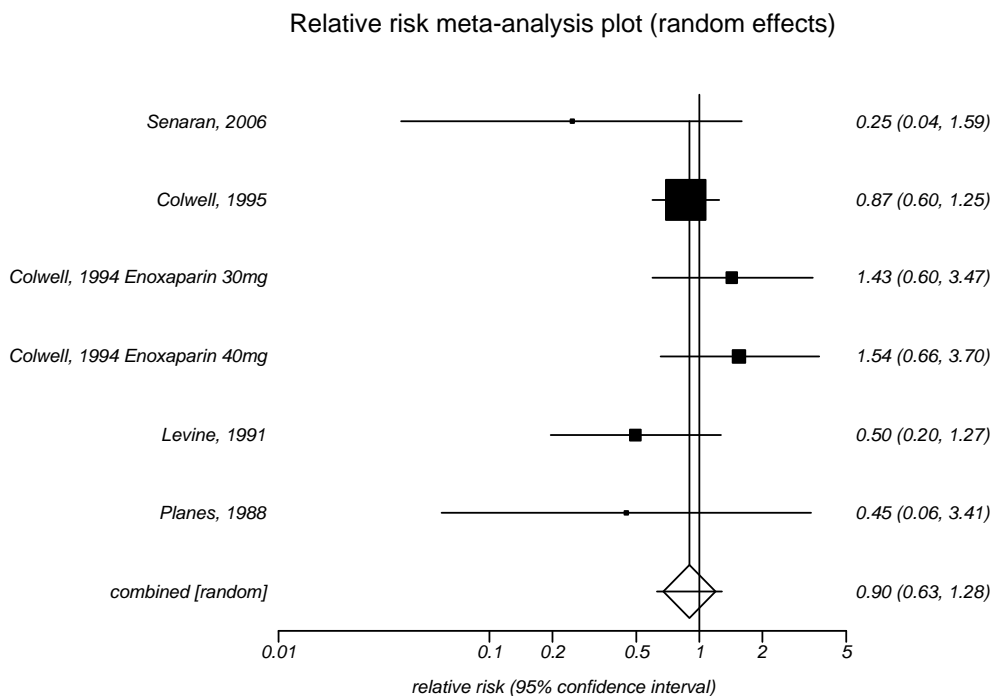
Figure 176. Impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on major bleeding leading to reoperation in patients who had major orthopedic surgery limited to total knee replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

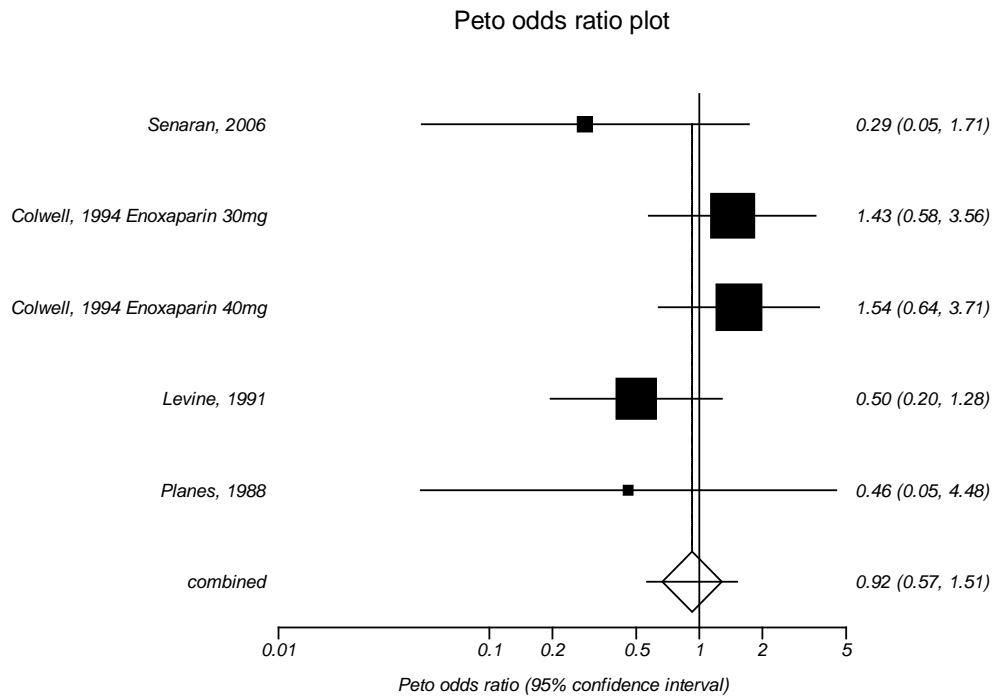
Figure 177. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on minor bleeding in patients undergoing major orthopedic surgery



I^2 : 9.9 percent
Egger's p-value: 0.608

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

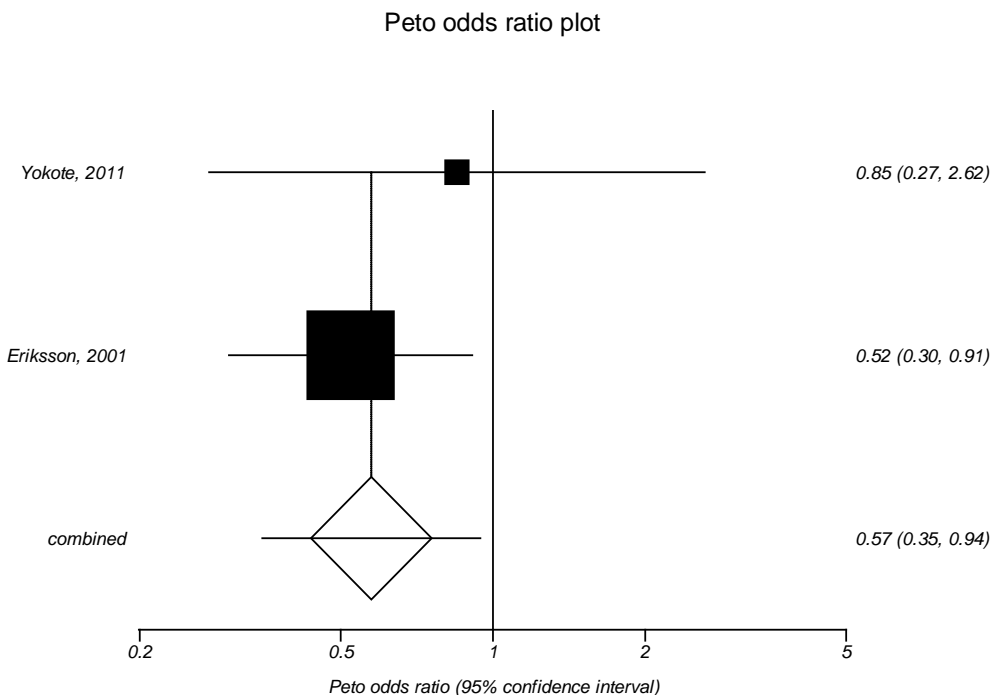
Figure 178. Impact of injectable low molecular weight heparin versus injectable unfractionated heparin on minor bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent
Egger's p-value: 0.132

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 179. Impact of injectable low molecular weight heparin versus injectable or factor Xa inhibitors on minor bleeding in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)

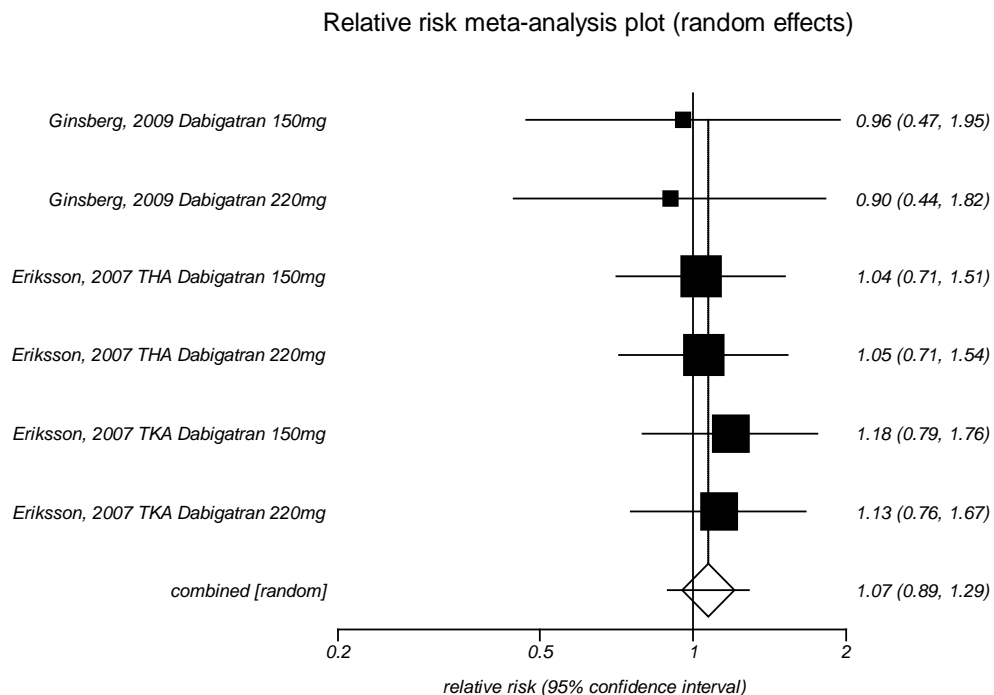


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

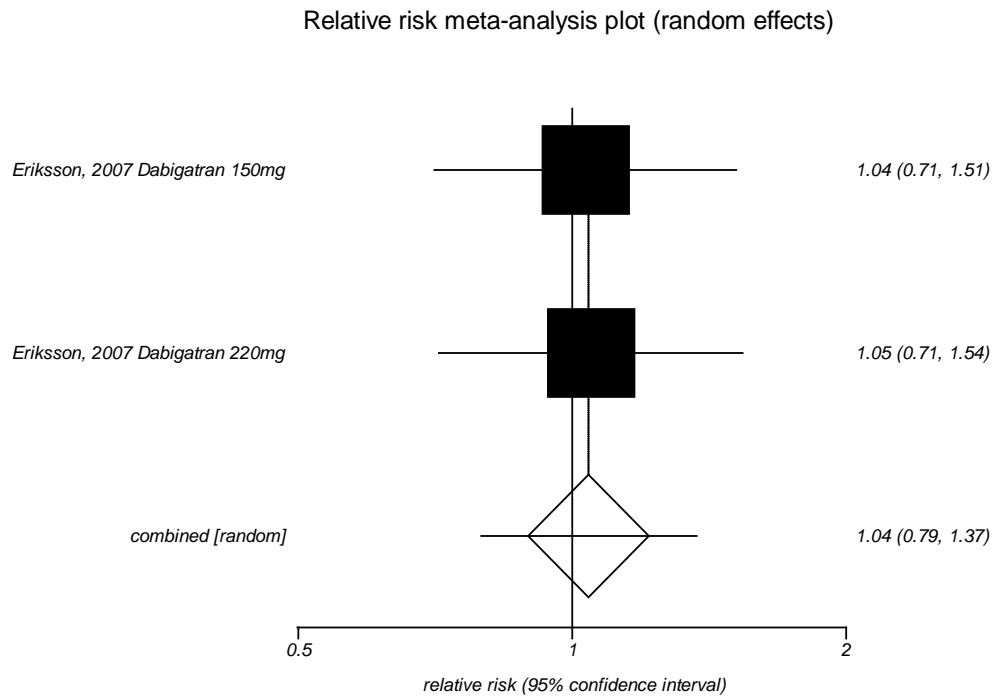
Figure 180. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on minor bleeding in patients undergoing major orthopedic surgery (same as analysis limited to trials published from 2001-present)



I^2 : 0 percent
Egger's p-value: 0.132

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

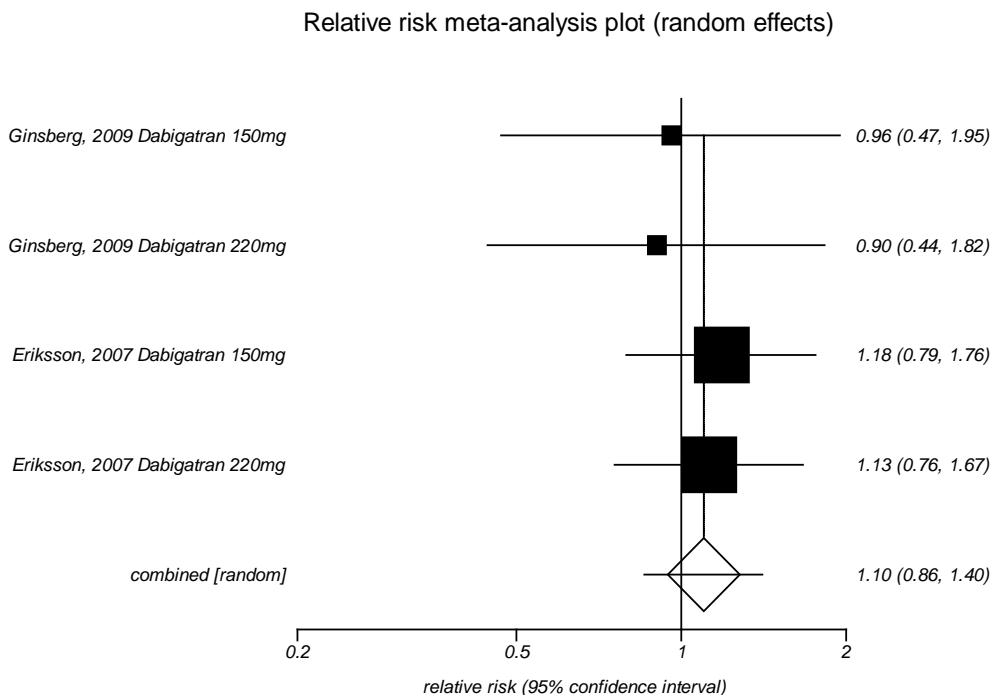
Figure 181. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on minor bleeding in patients undergoing major orthopedic surgery limited to total hip replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 182. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on minor bleeding in patients undergoing major orthopedic surgery limited to total knee replacement

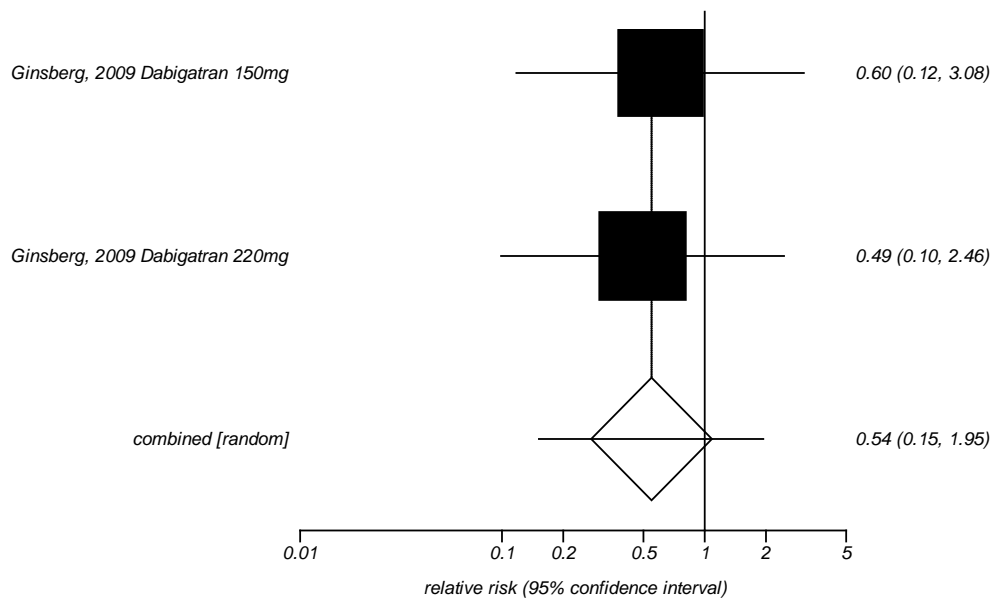


I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 183. Impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on minor bleeding during the postdischarge period in patients who had total knee replacement surgery

Relative risk meta-analysis plot (random effects)

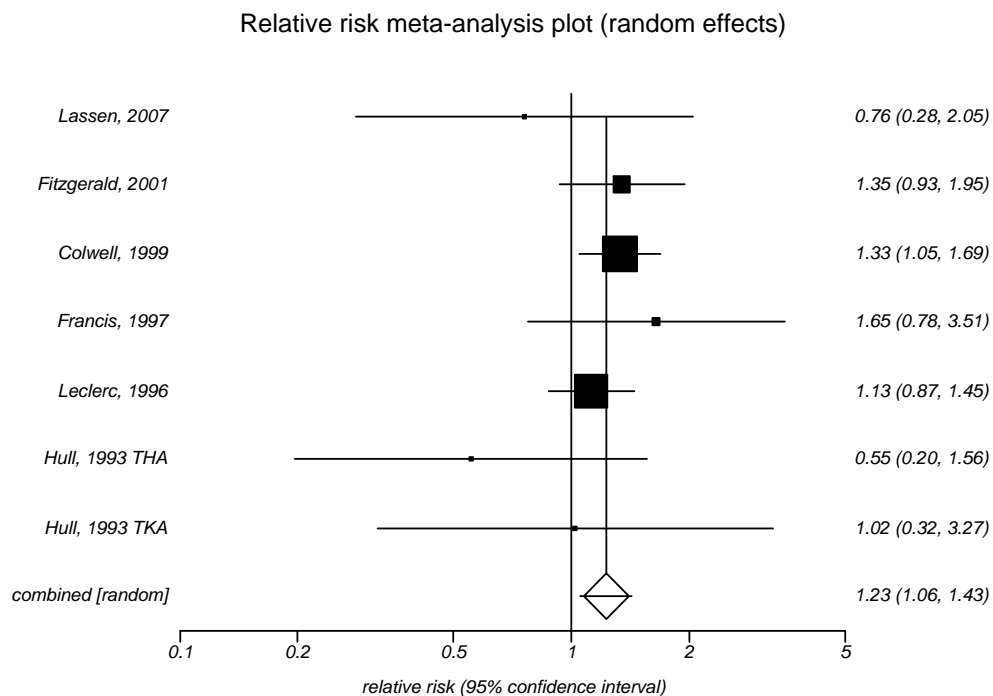


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 184. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding in patients undergoing major orthopedic surgery

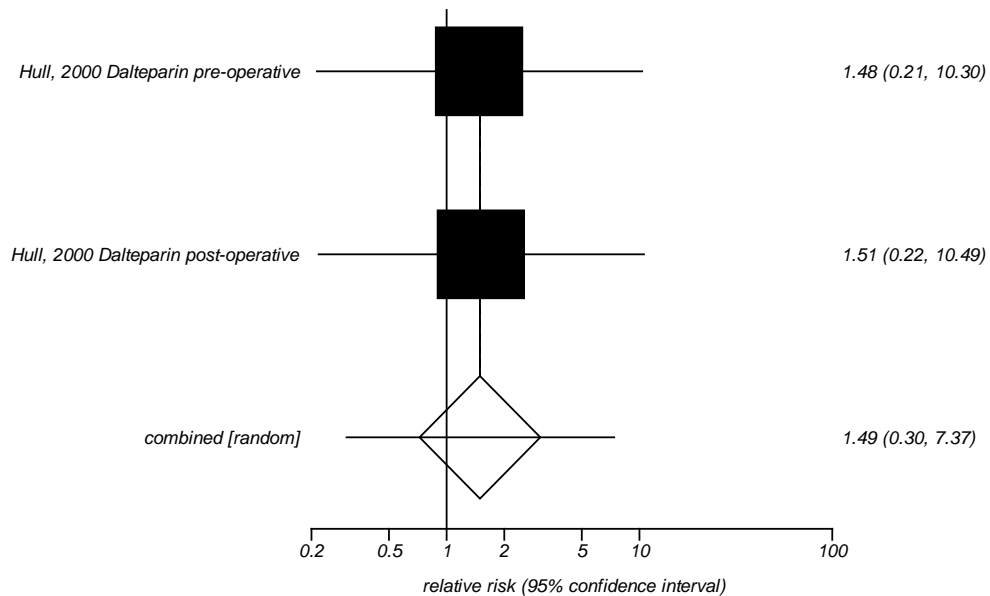


I^2 : 0 percent
Egger's p-value: 0.311

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 185. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding during days 0 to 1 in patients who had total hip replacement surgery

Relative risk meta-analysis plot (random effects)



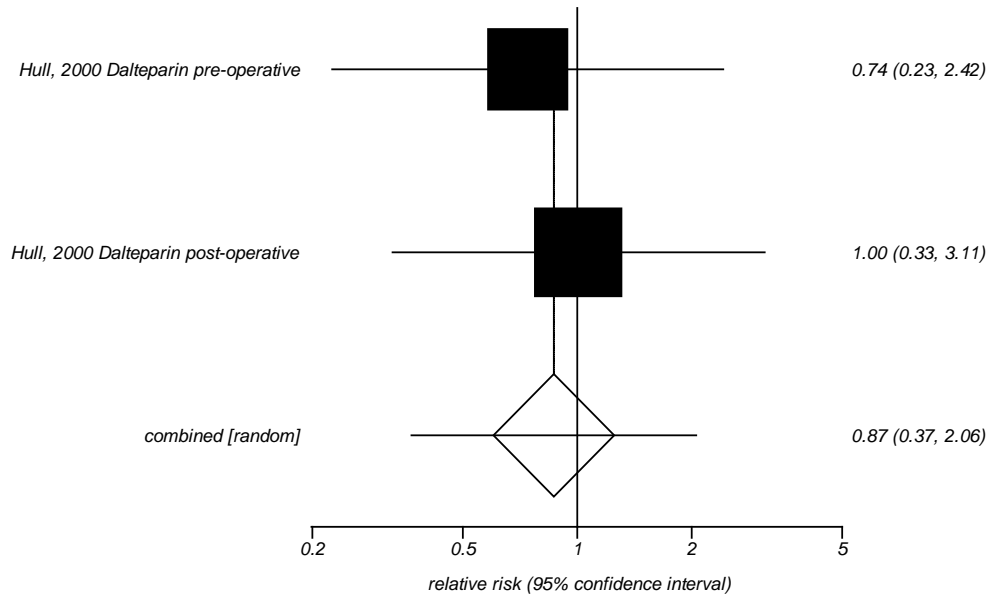
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 186. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding during days 2 to 8 in patients who had total hip replacement surgery

Relative risk meta-analysis plot (random effects)



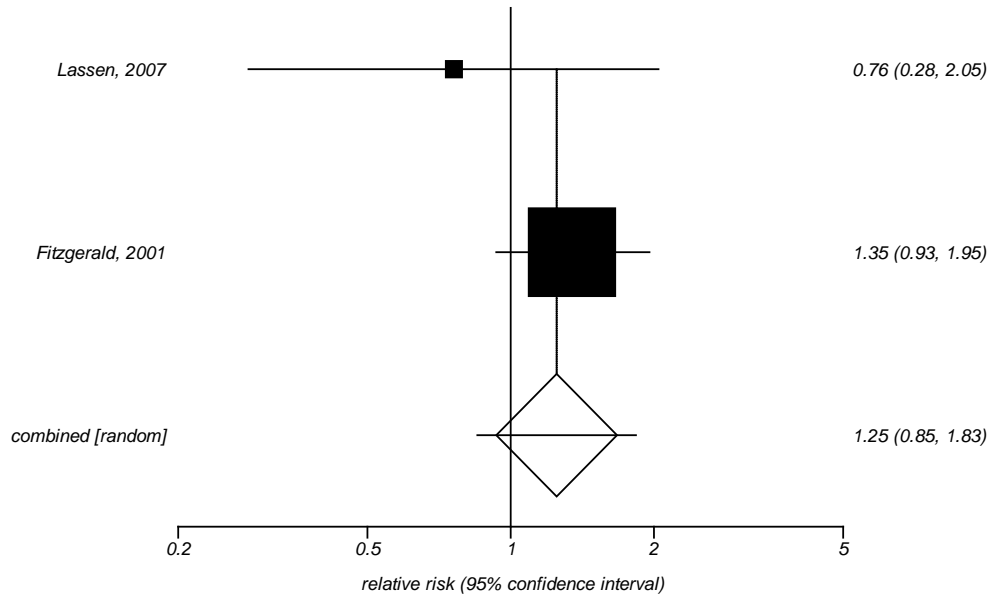
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 187. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding in patients undergoing major orthopedic surgery limited to trials published from 2001-present

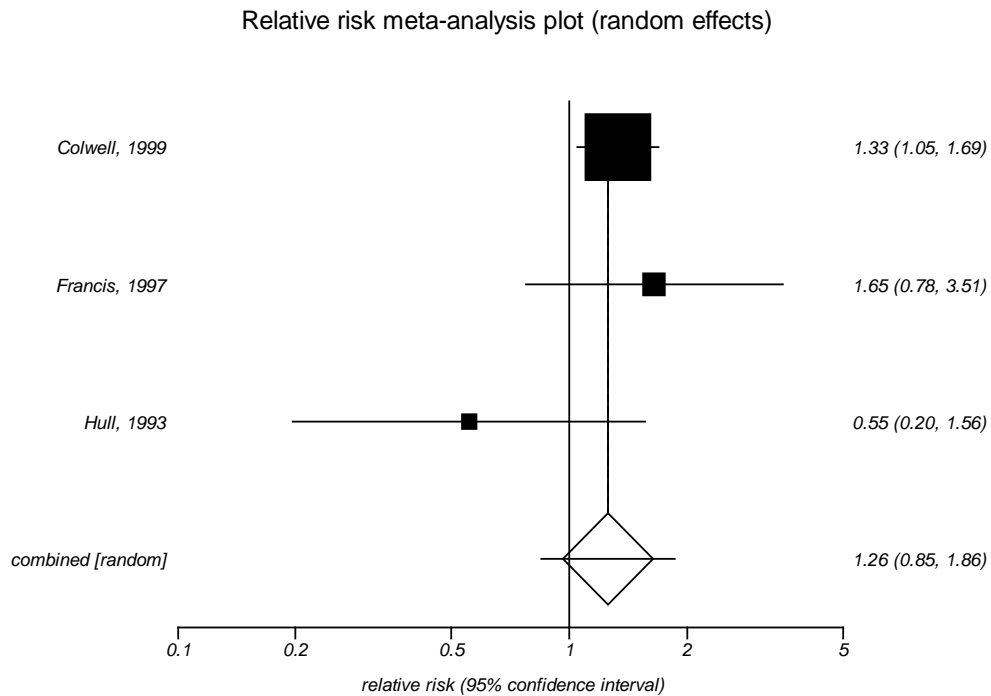
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

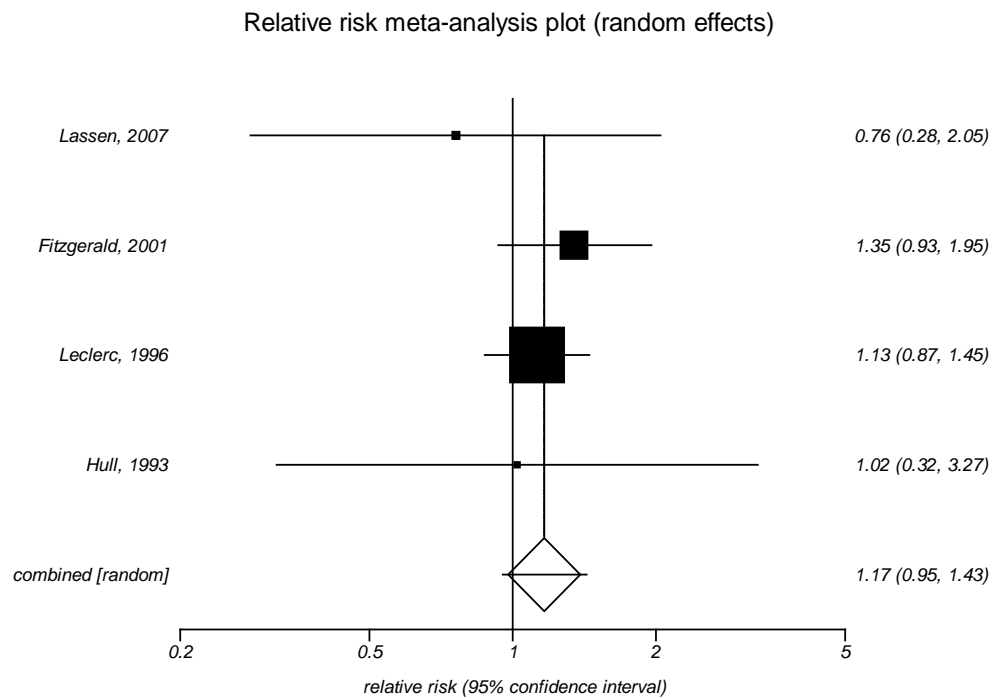
Figure 188. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery



I^2 : 27.8 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

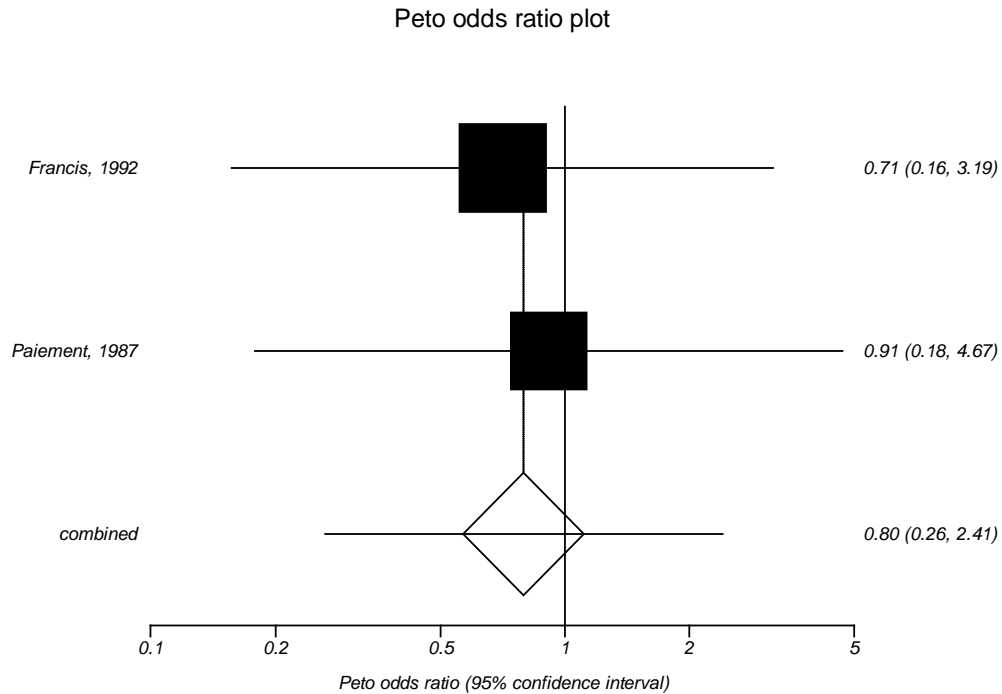
Figure 189. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on minor bleeding in patients undergoing major orthopedic surgery limited to total knee replacement



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 190. Impact of oral vitamin K antagonists versus mechanical prophylaxis on minor bleeding in patients undergoing major orthopedic surgery (same as analysis limited to total hip replacement)

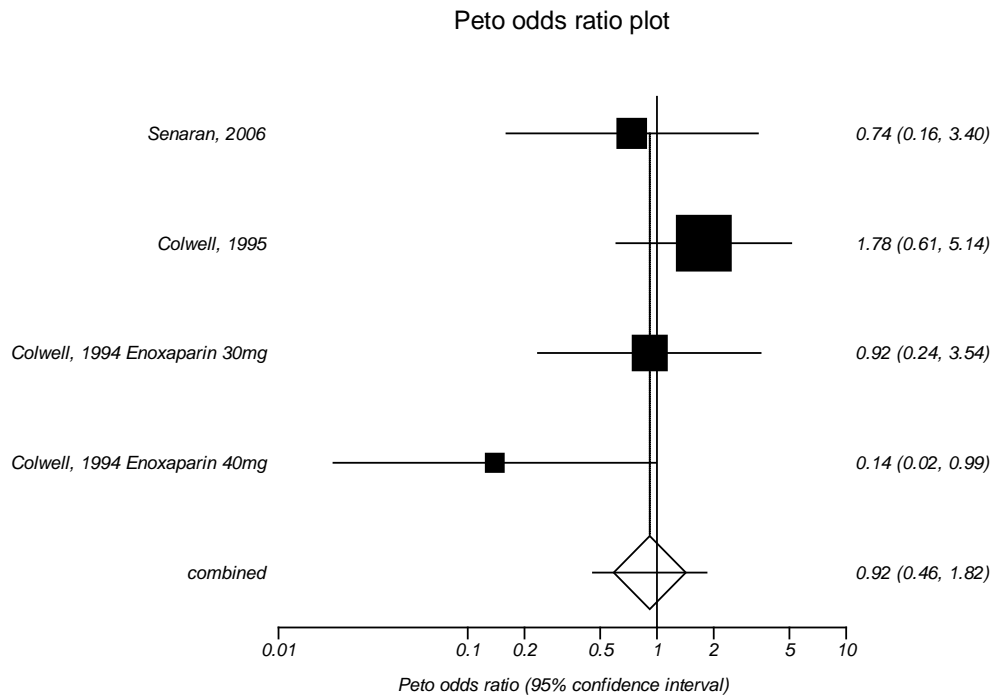


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

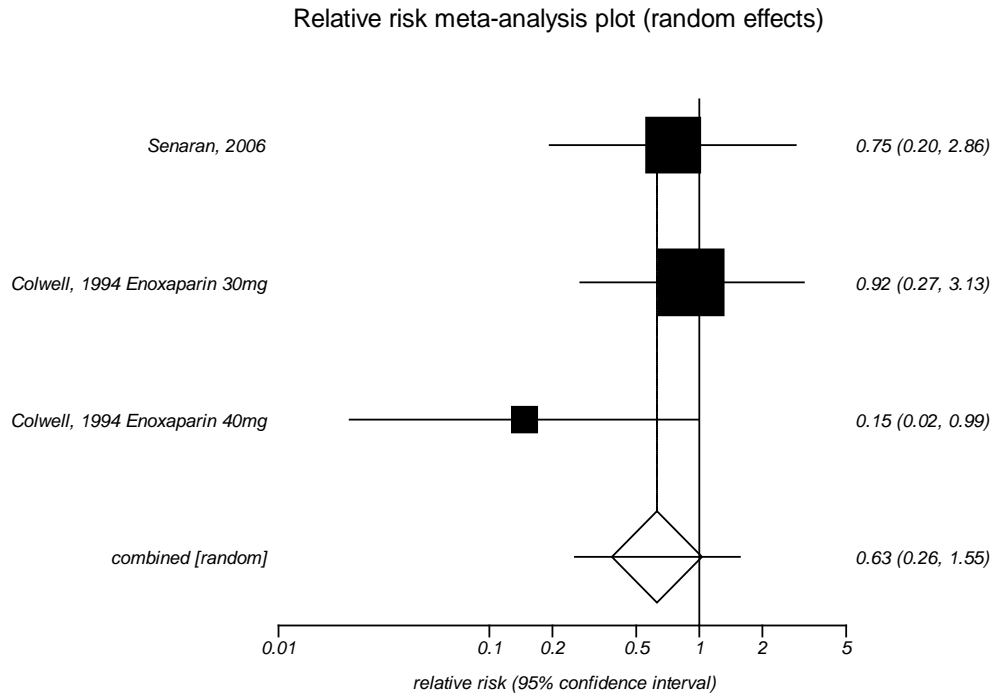
Figure 191. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on surgical site bleeding in patients undergoing major orthopedic surgery



I^2 : 41.4 percent
 Egger's p-value: 0.021

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 192. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on surgical site bleeding in patients undergoing major orthopedic surgery limited to total hip replacement surgery

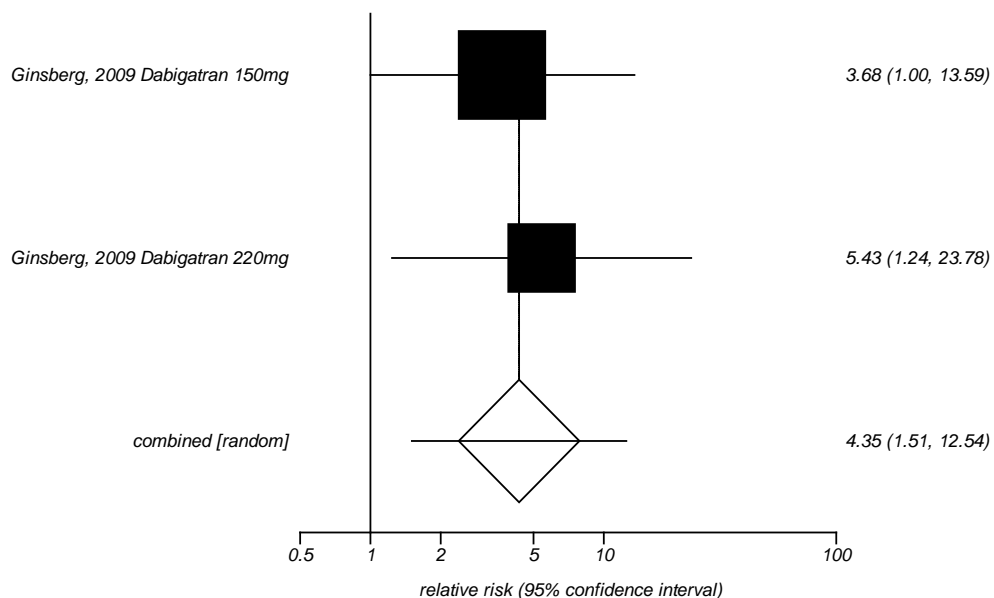


I^2 : 3.1 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 193. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on surgical site bleeding in patients undergoing major orthopedic surgery (same as 2001-present, same as limited to total knee replacement)

Relative risk meta-analysis plot (random effects)

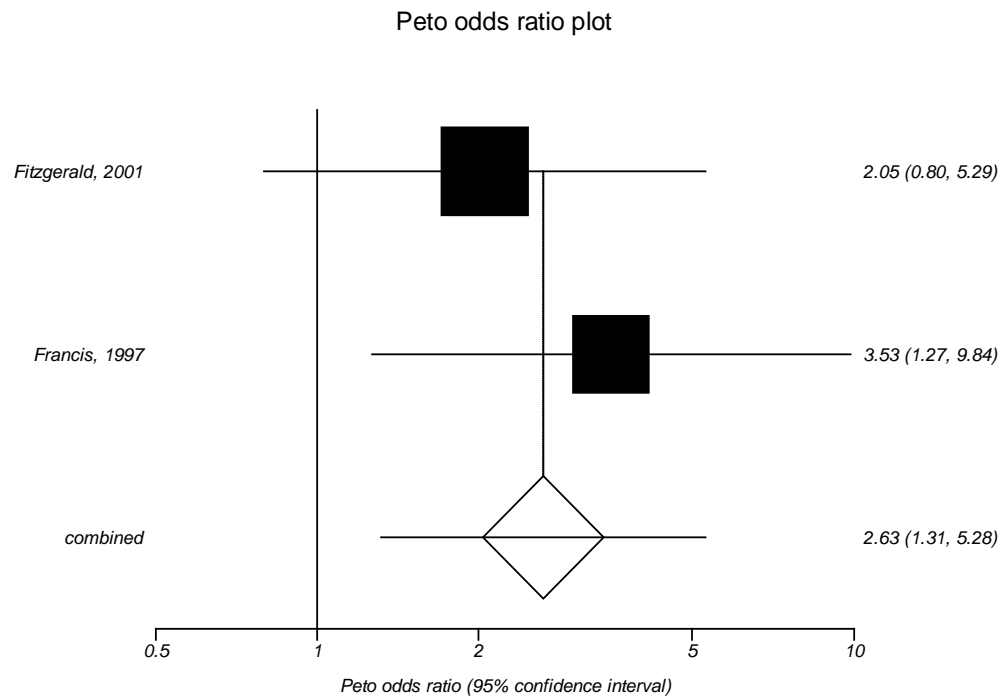


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 194. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on surgical site bleeding in patients undergoing major orthopedic surgery

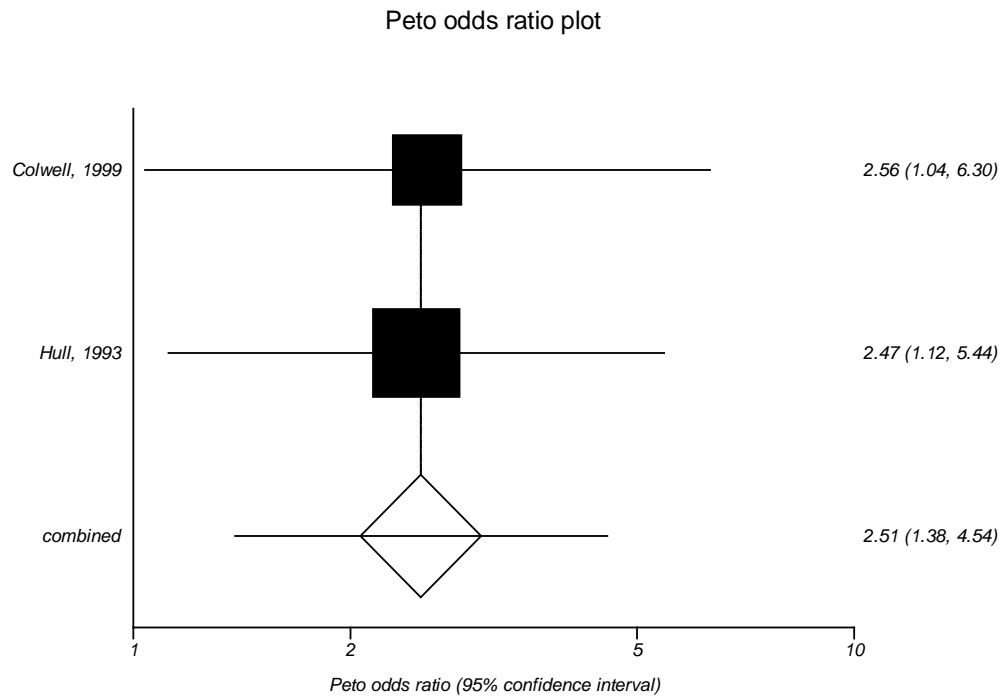


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 195. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on major surgical site bleeding in patients undergoing major orthopedic surgery



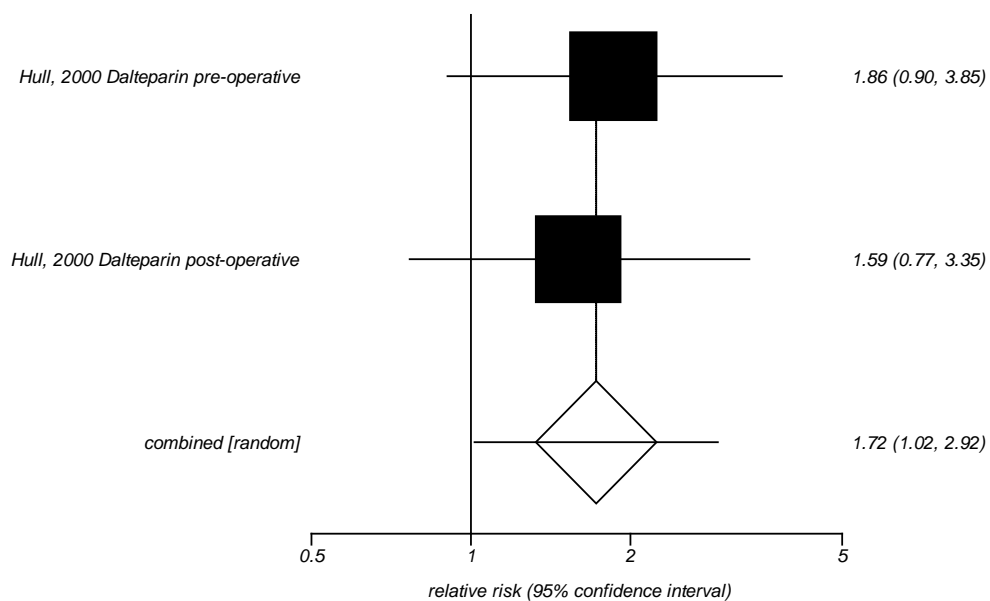
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 196. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major surgical site bleeding during days 0 to 1 in patients who had total hip replacement surgery

Relative risk meta-analysis plot (random effects)

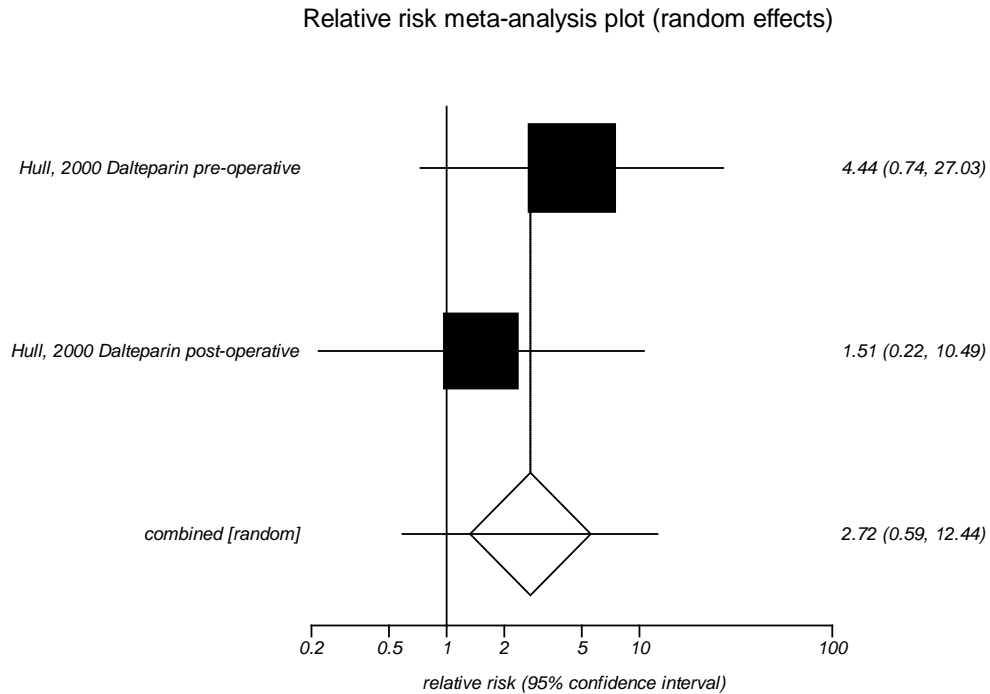


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 197. Impact of injectable low molecular weight heparin versus oral vitamin K antagonists on major surgical site bleeding during days 2 to 8 in patients who had total hip replacement surgery

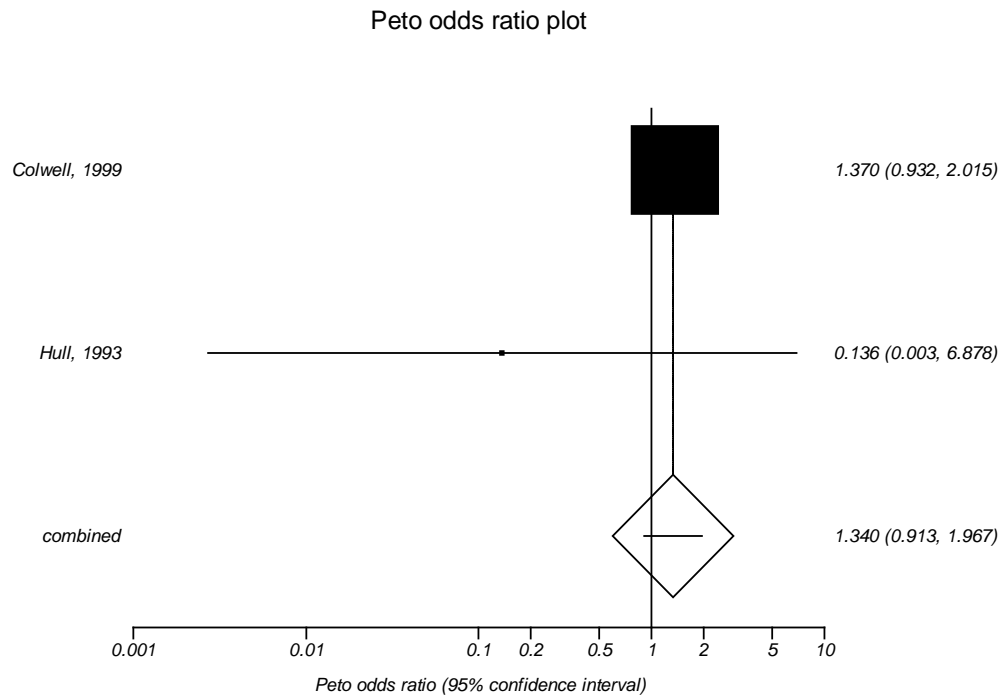


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 198. Impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on minor surgical site bleeding in patients undergoing major orthopedic surgery



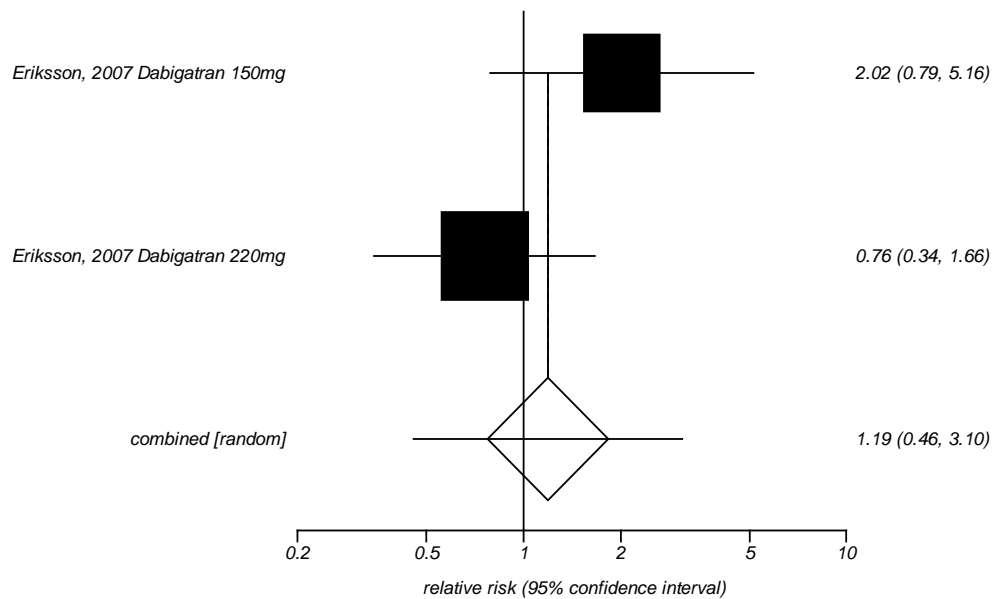
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 199. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery limited to total hip replacement surgery

Relative risk meta-analysis plot (random effects)

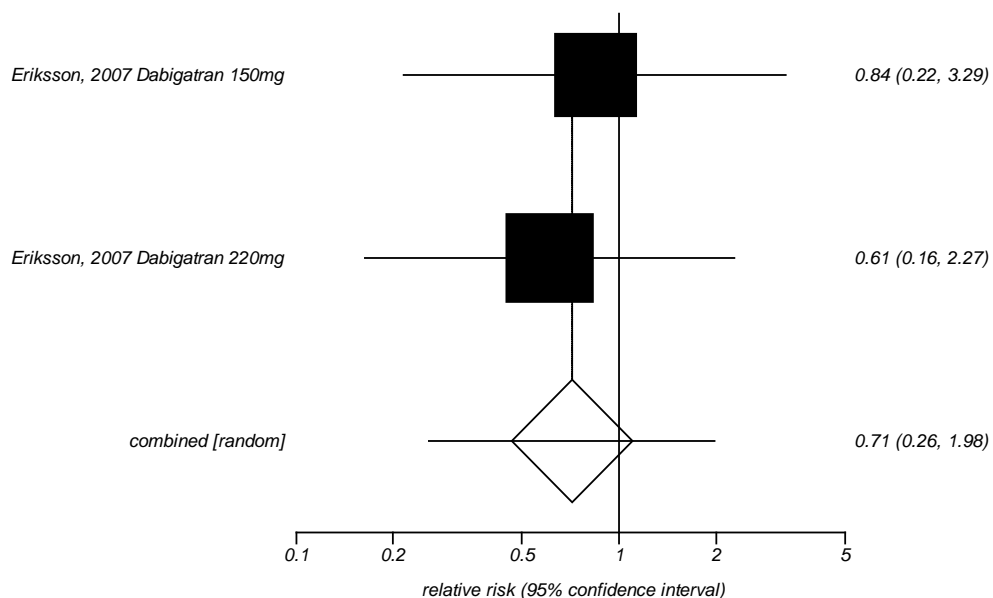


I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 200. Impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery limited to total knee replacement surgery

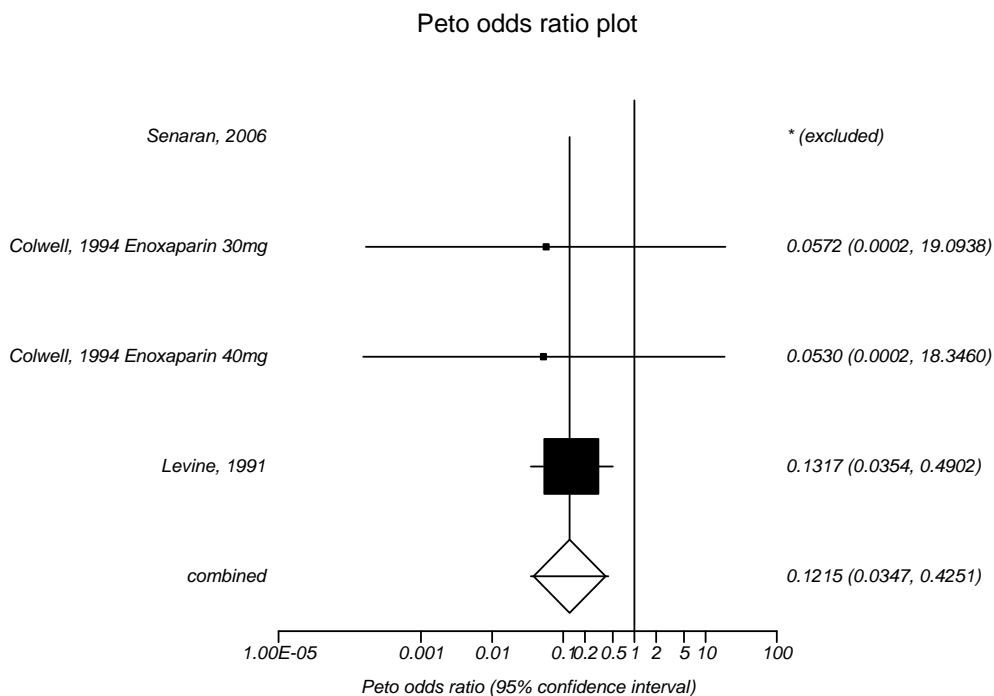
Relative risk meta-analysis plot (random effects)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

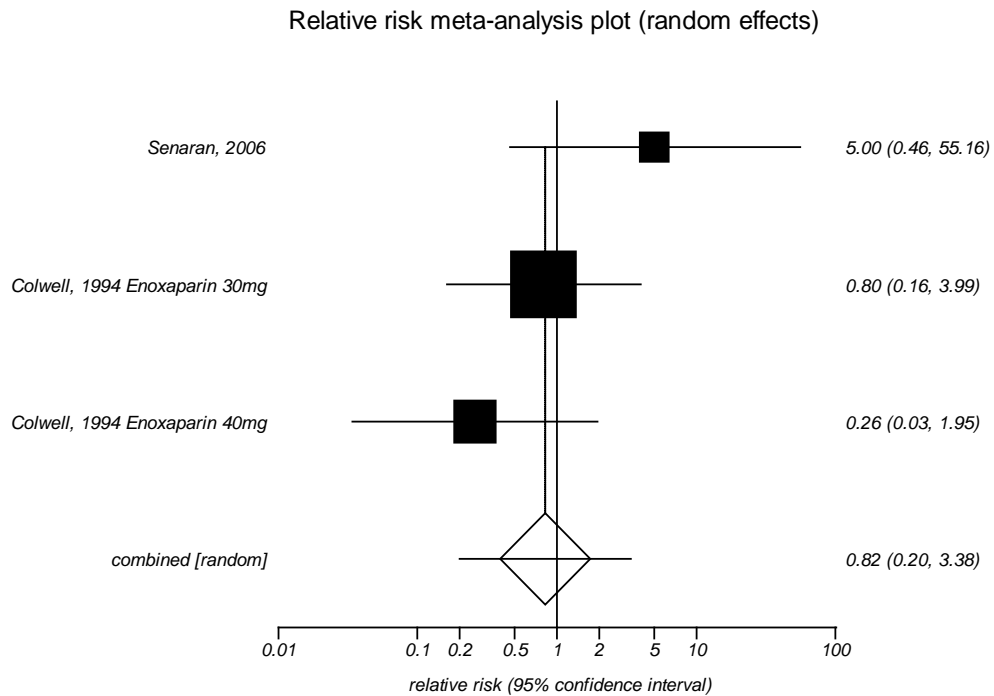
Figure 201. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on heparin-induced thrombocytopenia in patients who had major orthopedic surgery (same as analysis limited to total hip replacement surgery)



I^2 : 0 percent
 Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 202. Impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on readmission in patients who had major orthopedic surgery (same as analysis limited to total hip replacement surgery)

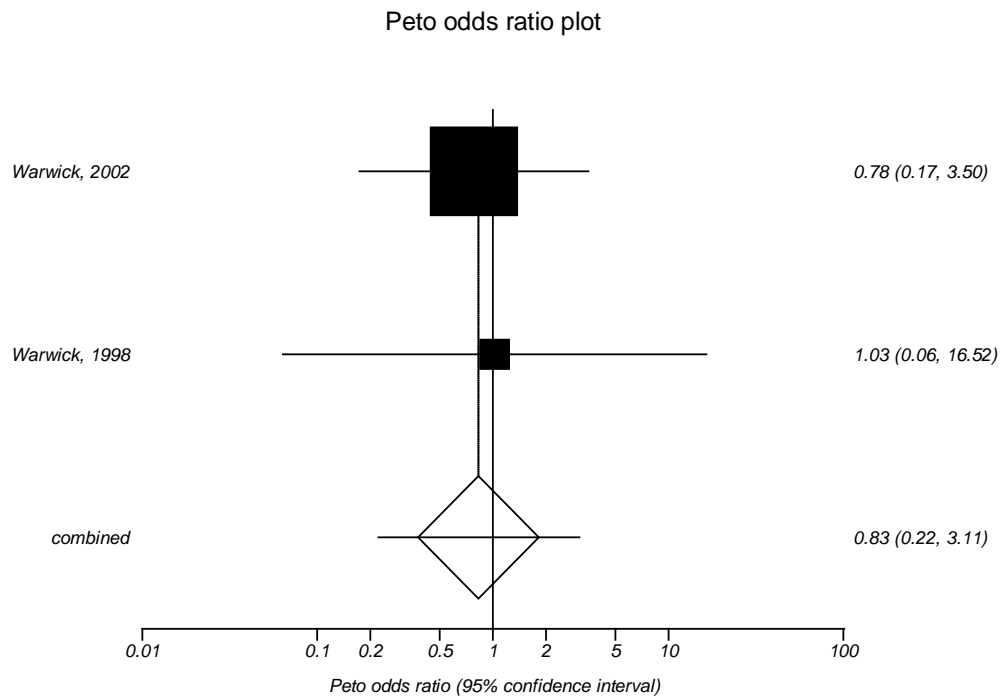


I^2 : 14.1 percent

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 203. Impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on readmission in patients who had major orthopedic surgery

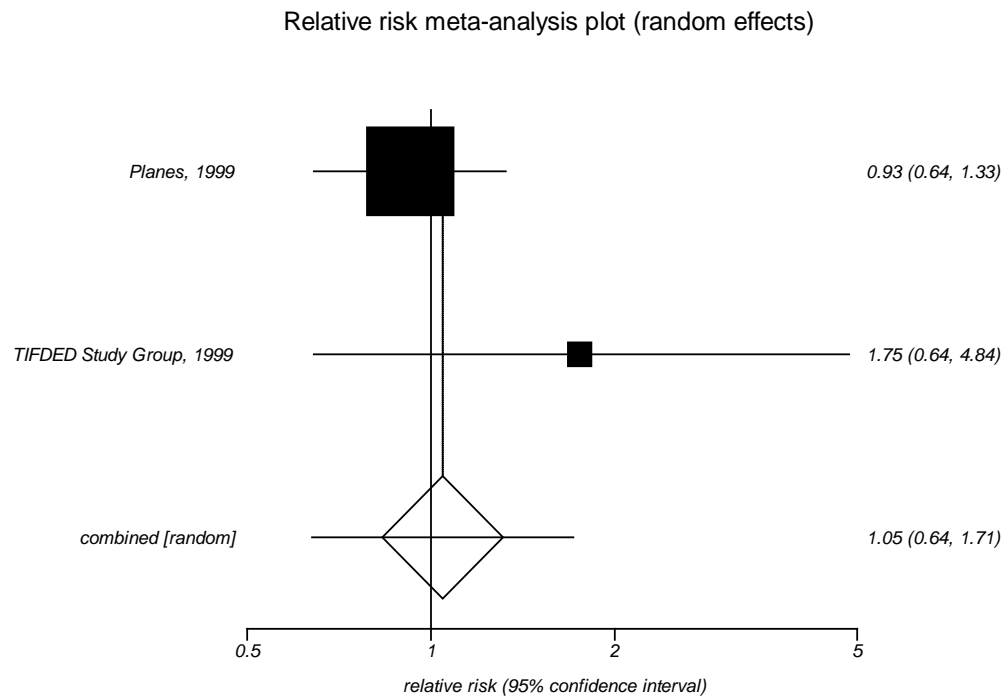


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 204. Impact of enoxaparin versus other low molecular weight heparin agents on deep vein thrombosis in patients who had major orthopedic surgery



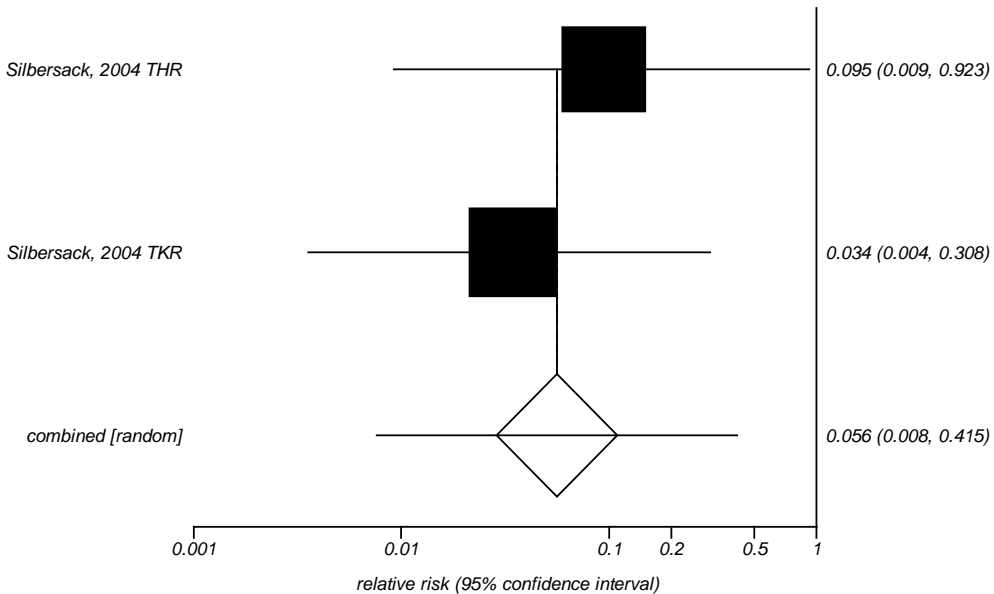
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 205. Impact of intermittent pneumatic compression versus graduated compression on deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)



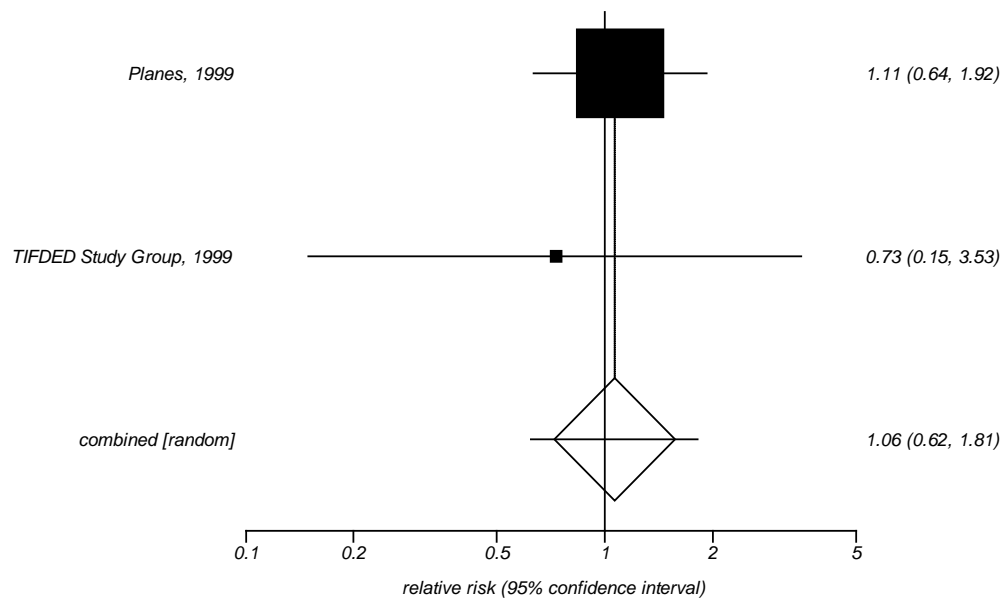
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 206. Impact of enoxaparin versus other low molecular weight heparin agents on proximal deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

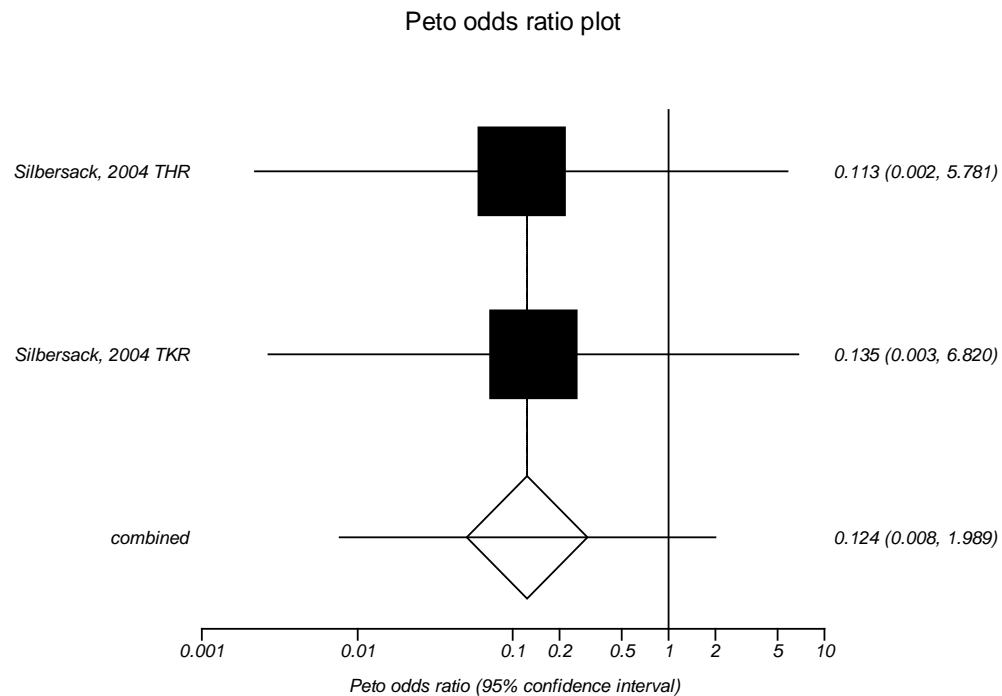


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 207. Impact of intermittent pneumatic compression versus graduated compression on proximal deep vein thrombosis in patients who had major orthopedic surgery



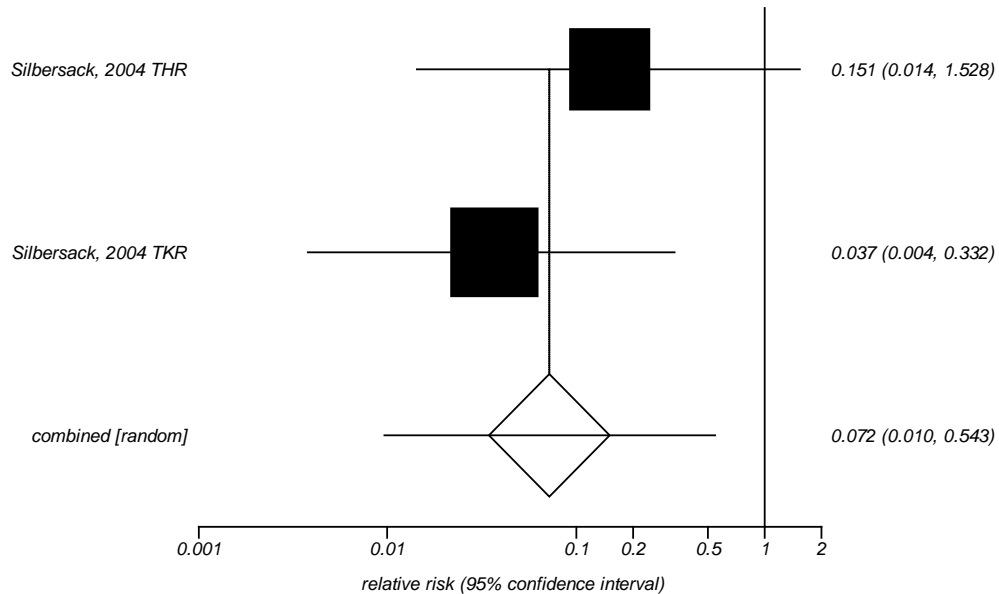
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 208. Impact of intermittent pneumatic compression versus graduated compression on distal deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

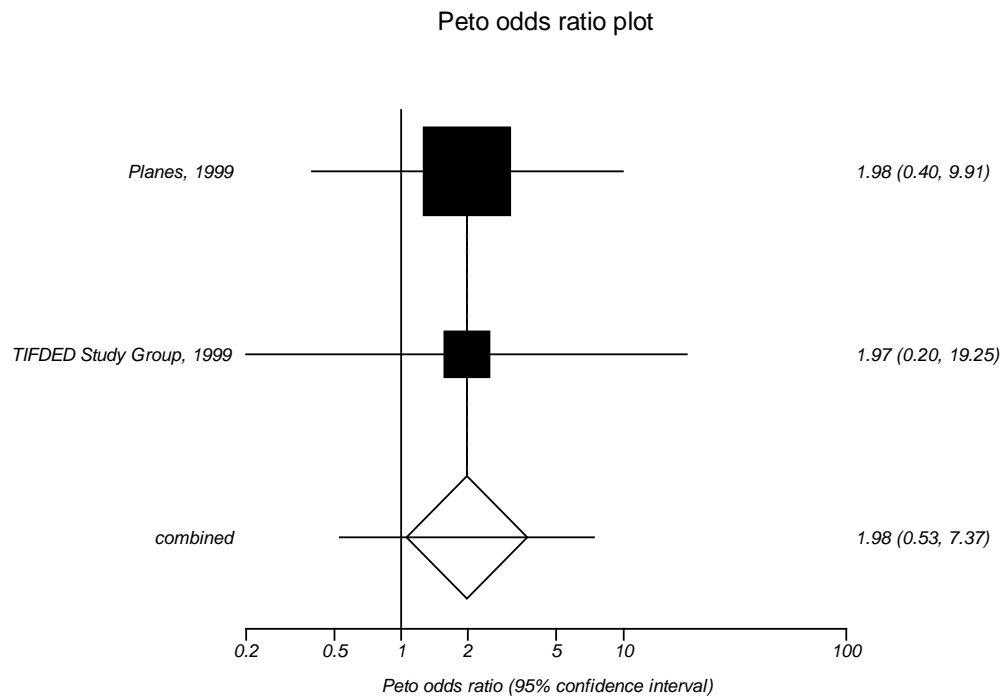


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 209. Impact of enoxaparin versus other low molecular weight heparin agents on major bleeding in patients who had major orthopedic surgery



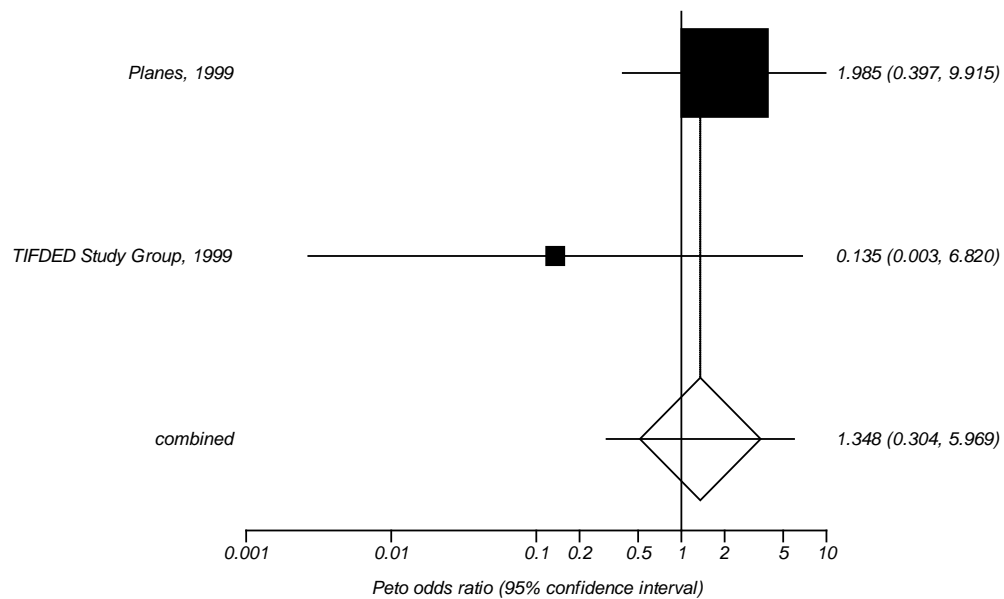
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 210. Impact of enoxaparin versus other low molecular weight heparin agents on surgical site bleeding in patients who had major orthopedic surgery

Peto odds ratio plot

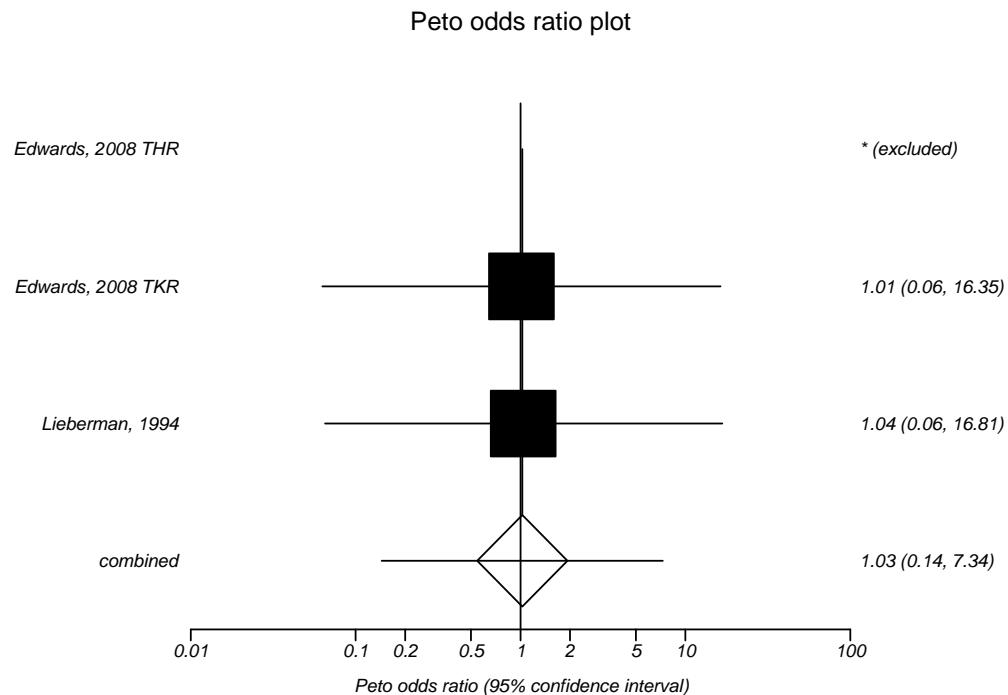


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 211. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on pulmonary embolism in patients who had major orthopedic surgery (same as the analysis of nonfatal pulmonary embolism)



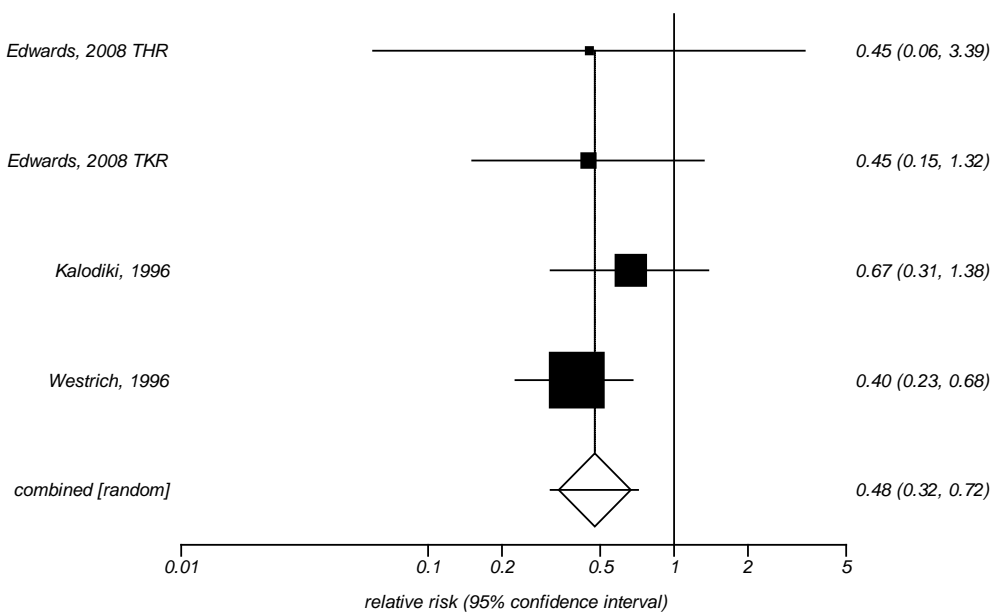
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 212. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)

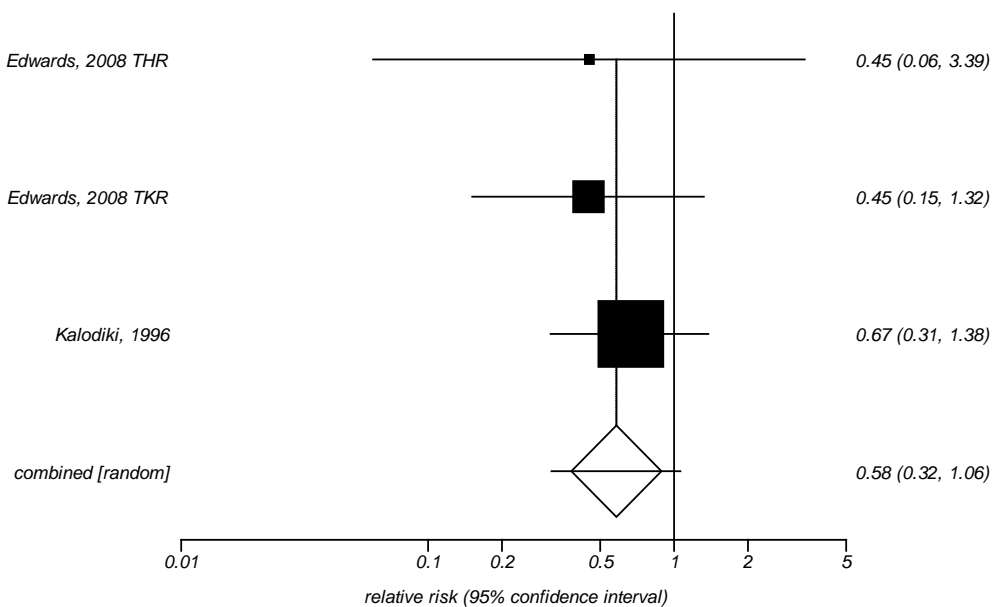


I^2 : 0 percent
Egger's p-value: 0.831

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 213. Impact of anticoagulant plus mechanical prophylaxis versus anticoagulant prophylaxis alone on deep vein thrombosis in patients who had major orthopedic surgery

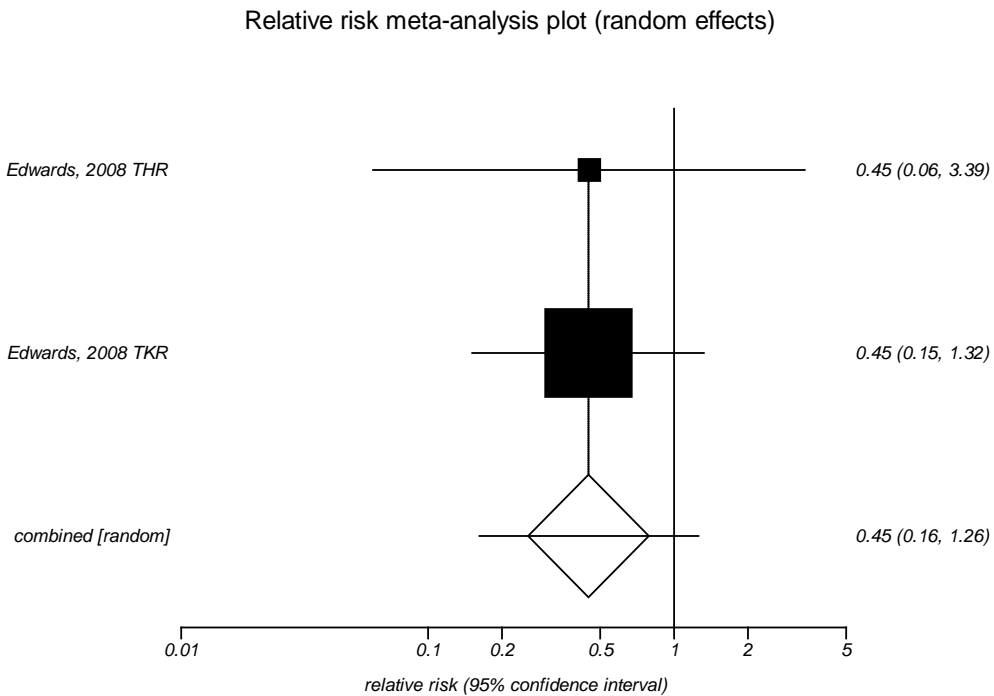
Relative risk meta-analysis plot (random effects)



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

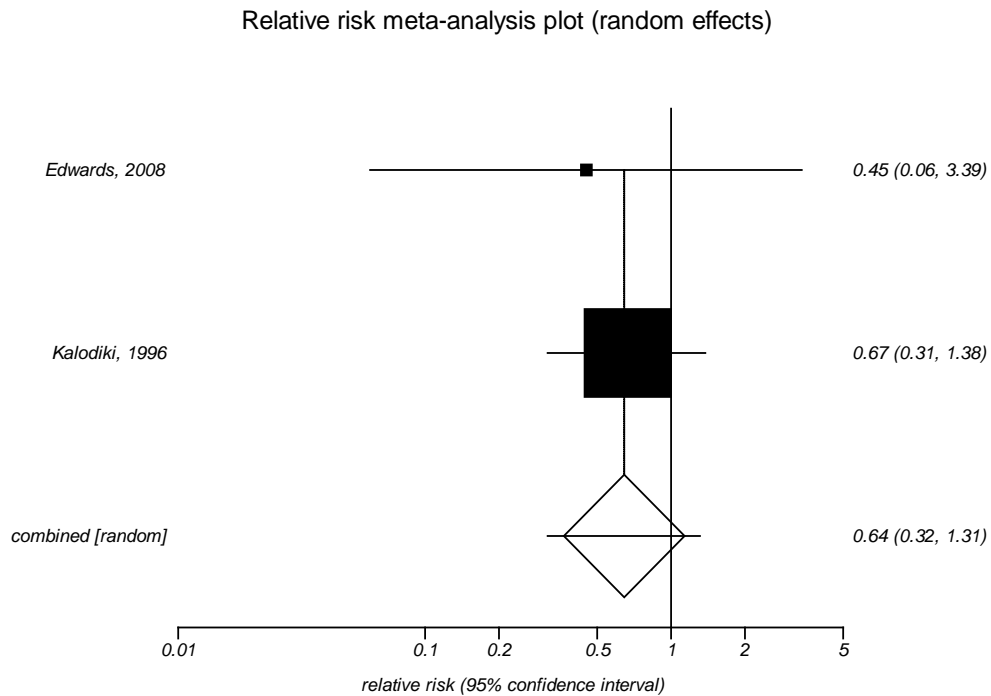
Figure 214. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

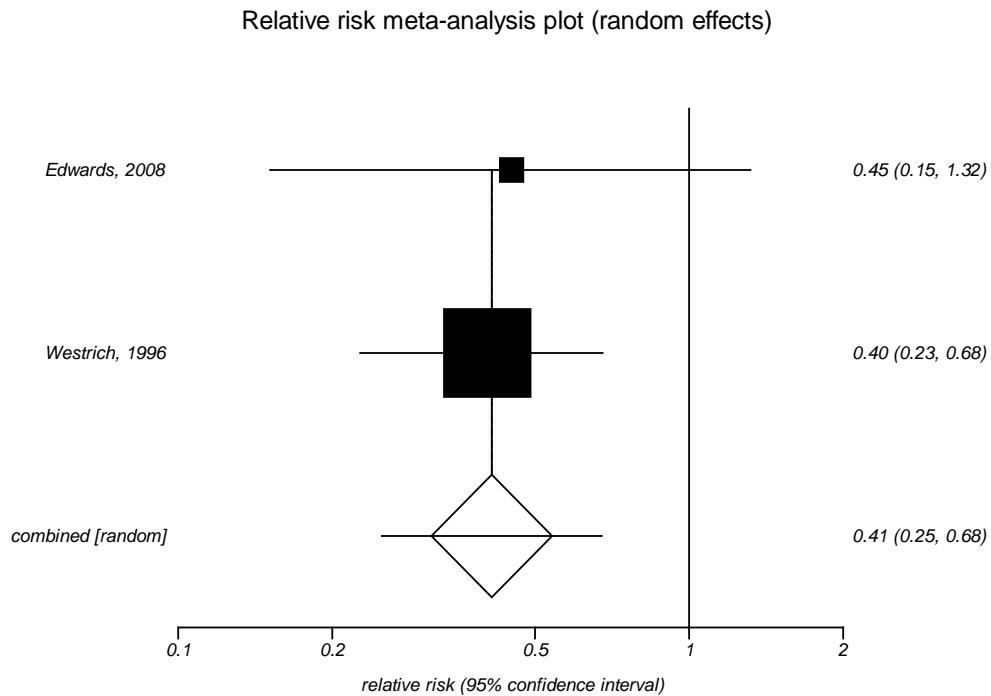
Figure 215. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

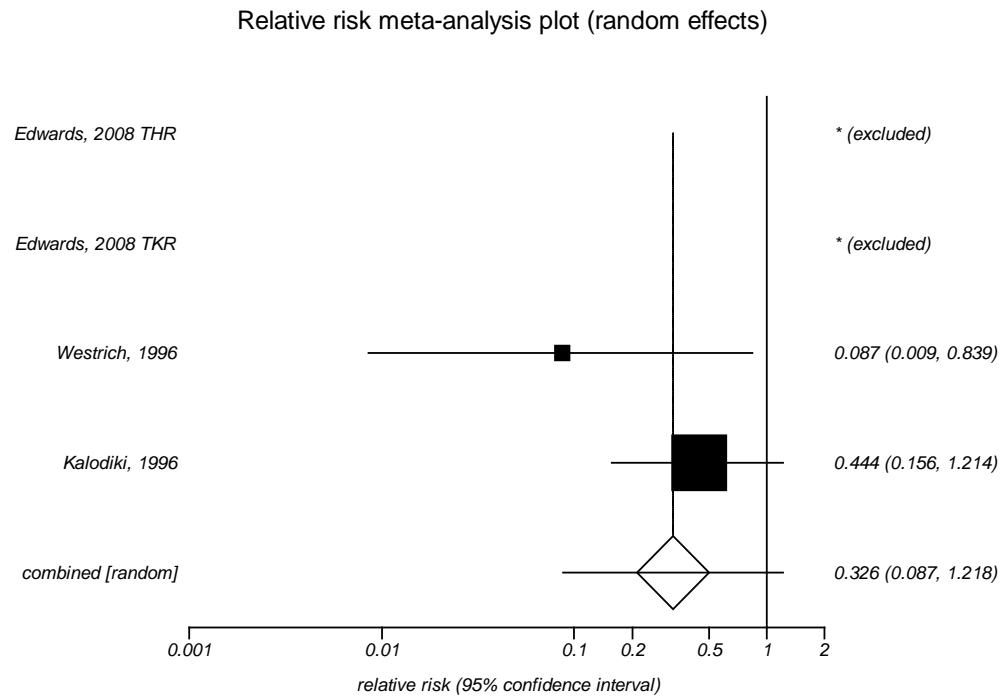
Figure 216. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on deep vein thrombosis in patients who had major orthopedic surgery limited to total knee replacement



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 217. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on proximal deep vein thrombosis in patients who had major orthopedic surgery



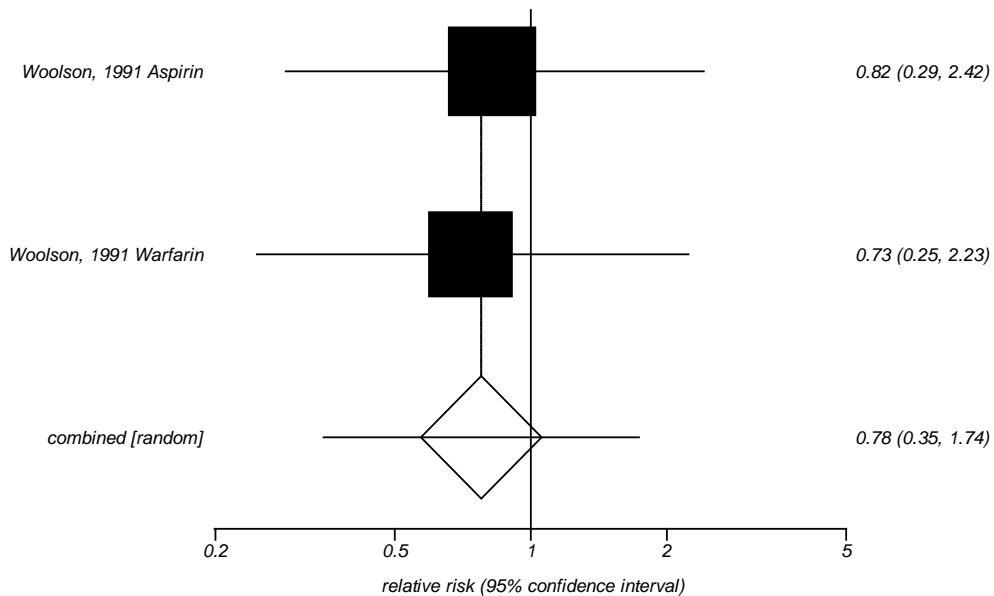
I²: Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 218. Impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone on proximal deep vein thrombosis in patients who had major orthopedic surgery

Relative risk meta-analysis plot (random effects)



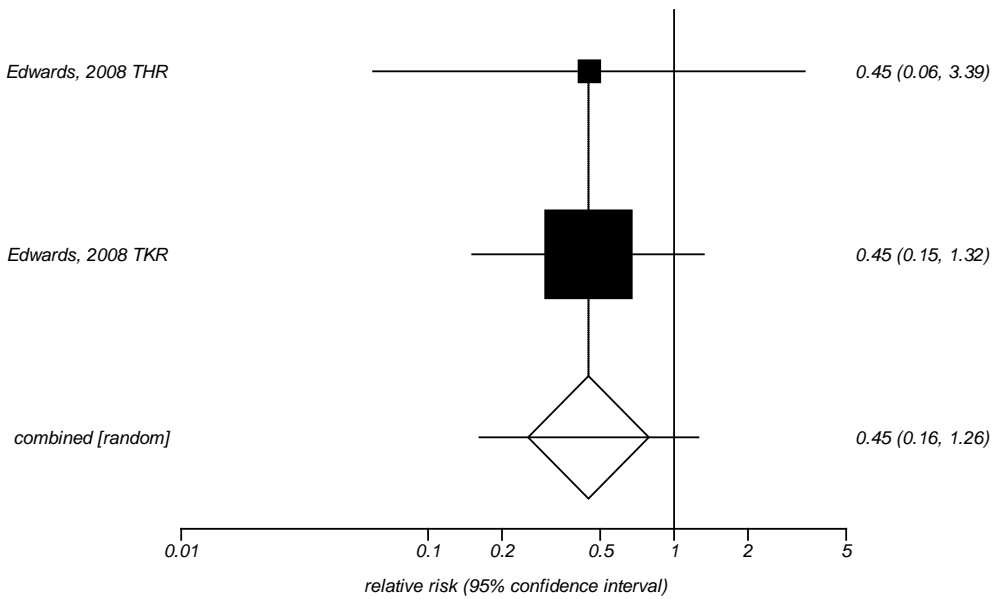
I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 219. Impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone on distal deep vein thrombosis in patients who had major orthopedic surgery (same as the analysis of trial published from 2001-present; same as the comparison of anticoagulant plus mechanical prophylaxis versus anticoagulant alone in patients who had major orthopedic surgery)

Relative risk meta-analysis plot (random effects)

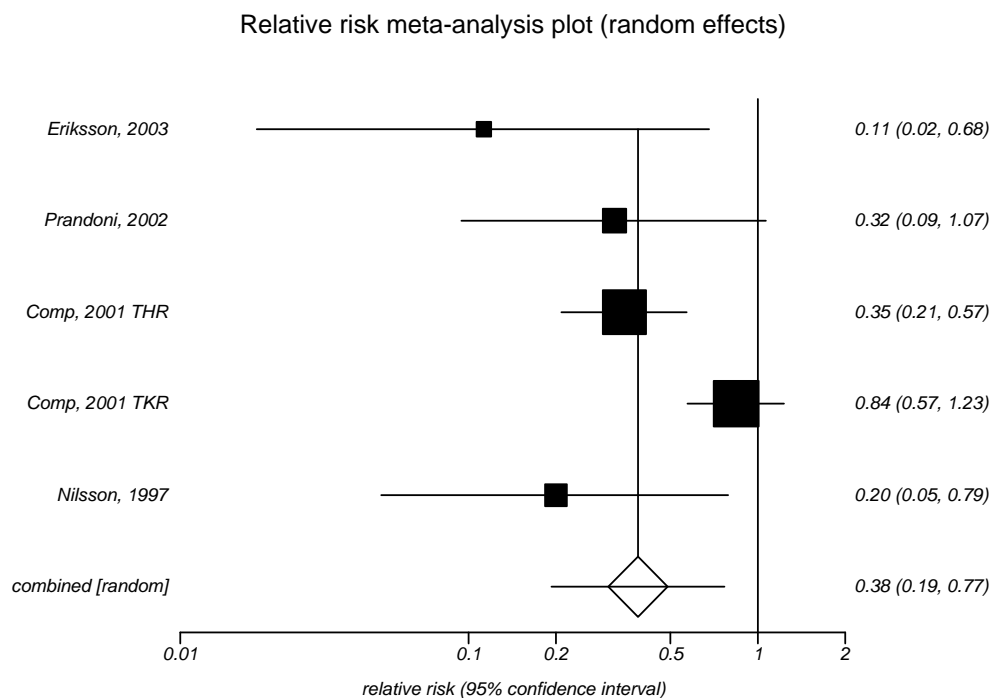


I^2 : Too few strata

Egger's p-value: Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

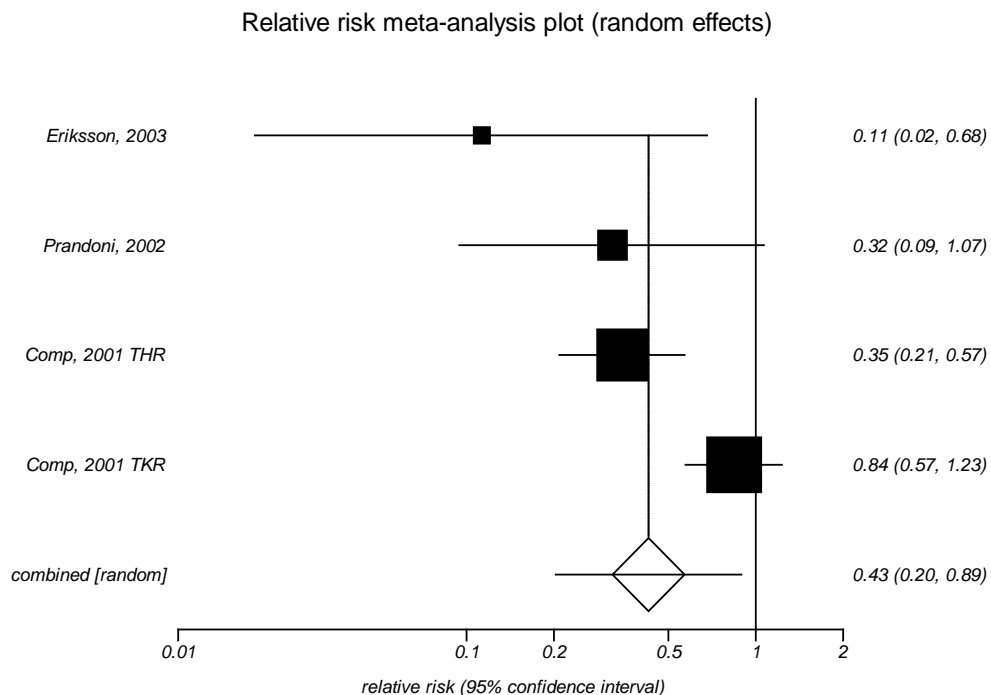
Figure 220. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery



I^2 : 69.1 percent
Egger's p-value: 0.150

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

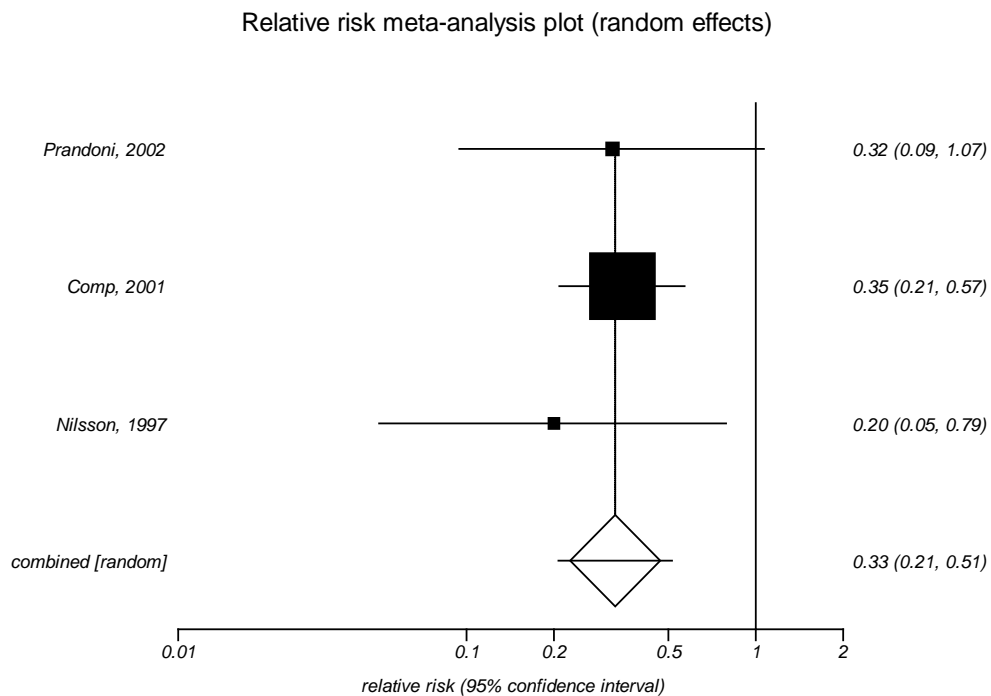
Figure 221. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery limited to trial published from 2001-present



I^2 : 72.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

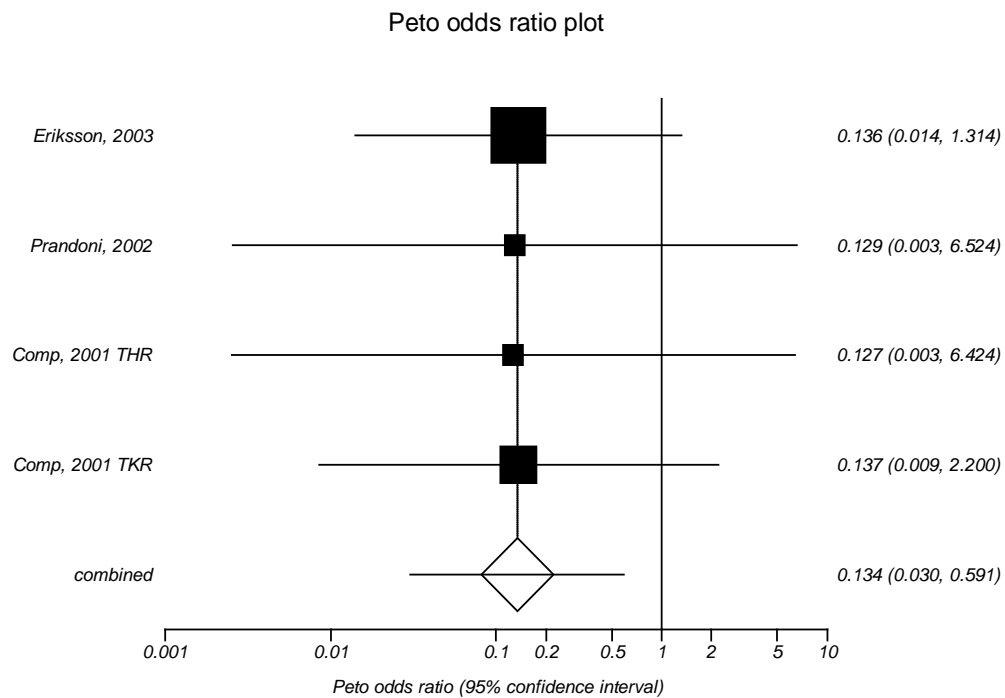
Figure 222. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

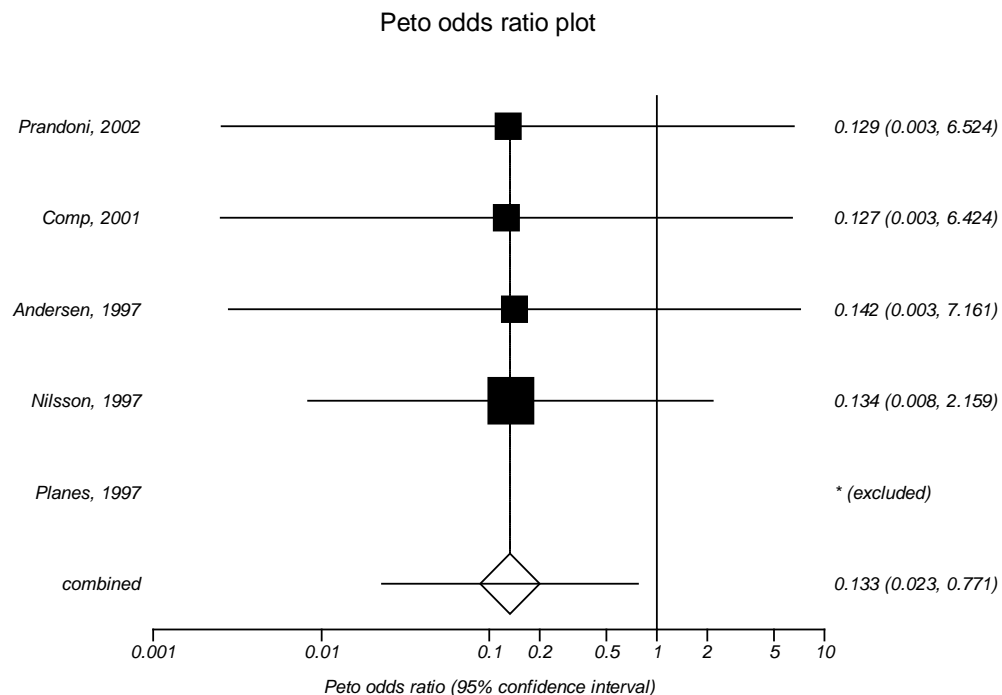
Figure 223. Impact of prolonged prophylaxis versus standard duration of prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

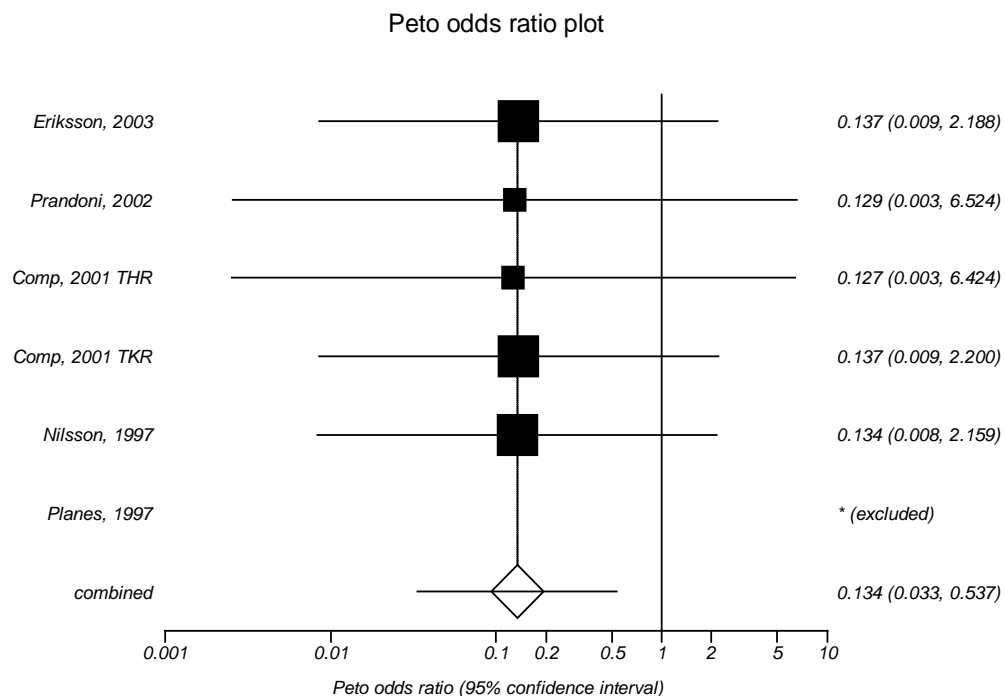
Figure 224. Impact of prolonged prophylaxis versus standard duration of prophylaxis on pulmonary embolism in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

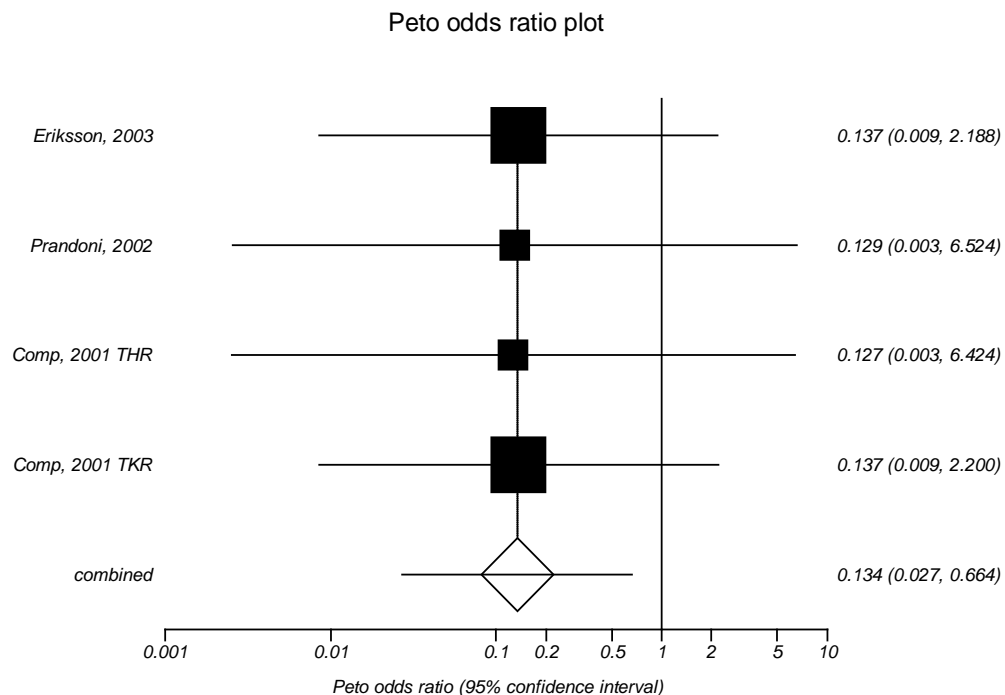
Figure 225. Impact of prolonged prophylaxis versus standard duration of prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery



I^2 : 0 percent
Egger's p-value: 0.016

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

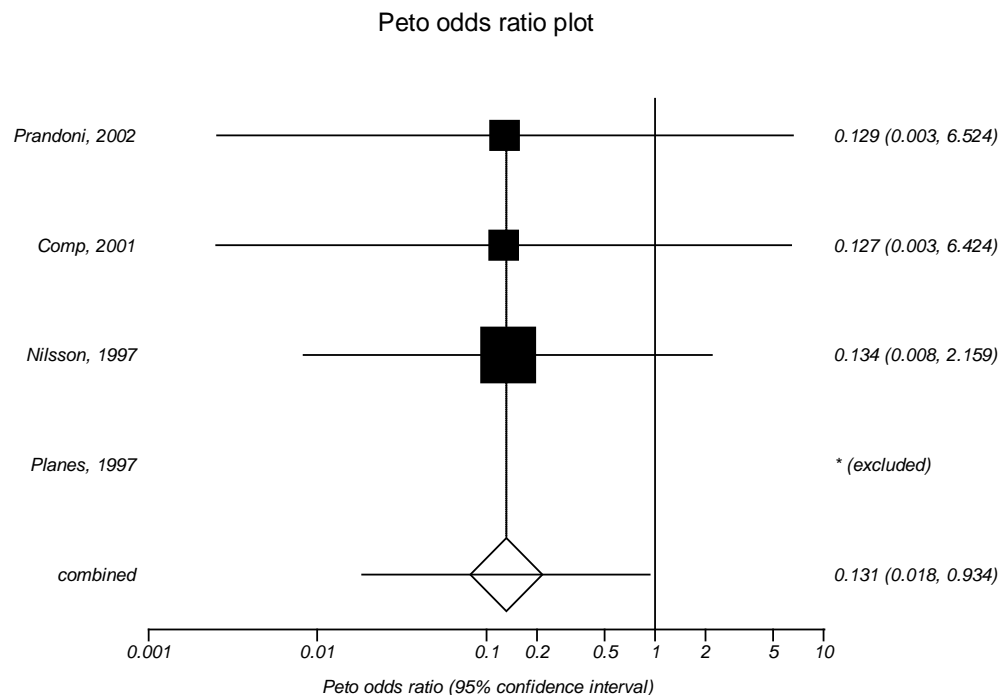
Figure 226. Impact of prolonged prophylaxis versus standard duration of prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

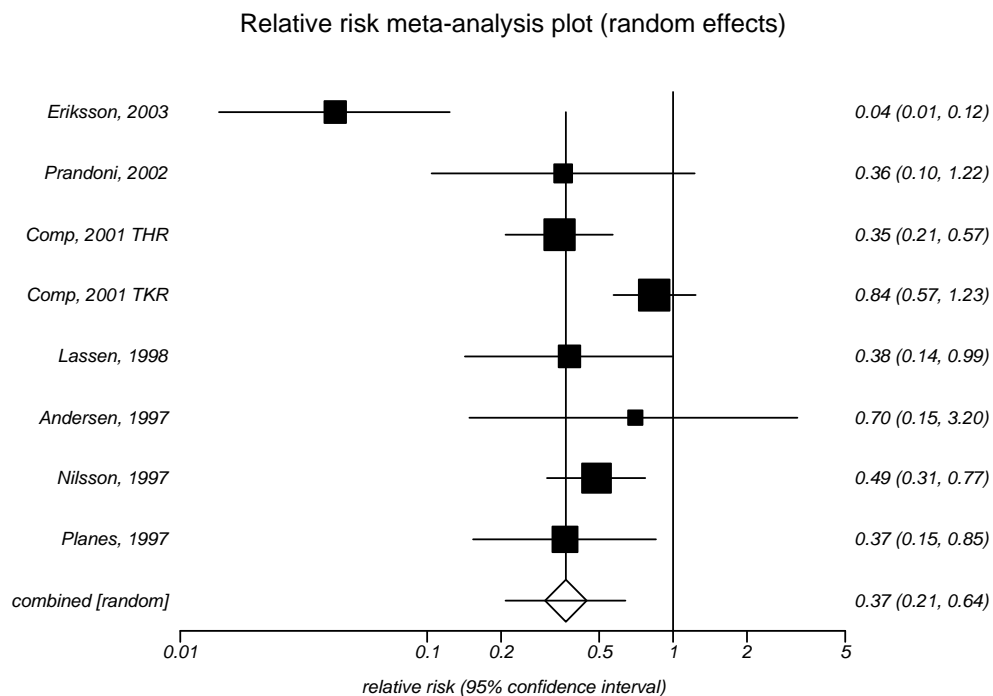
Figure 227. Impact of prolonged prophylaxis versus standard duration of prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

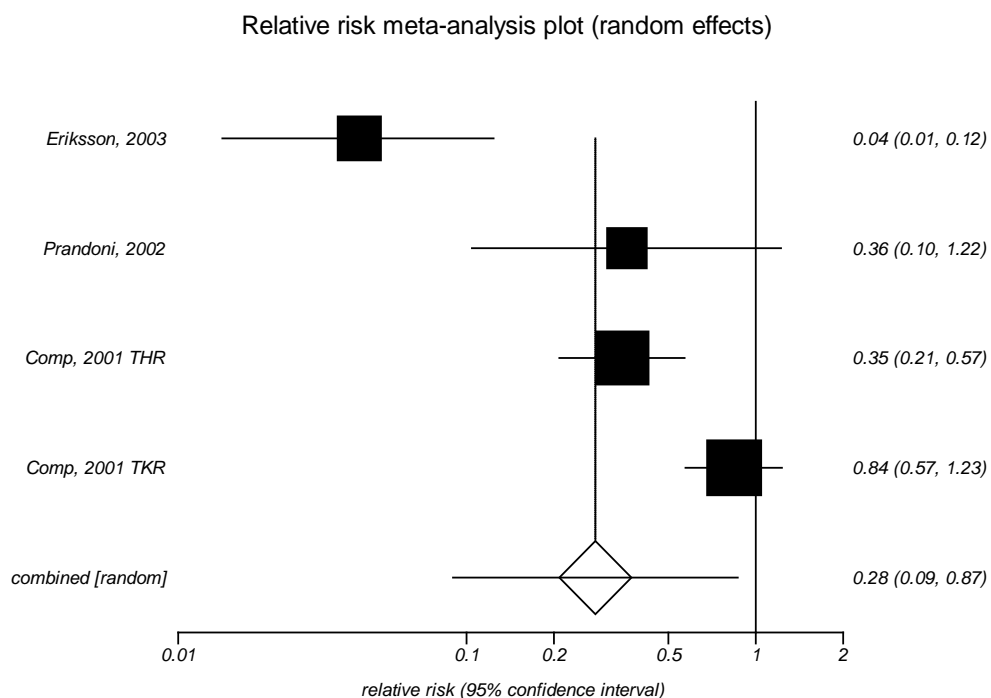
Figure 228. Impact of prolonged prophylaxis versus standard duration of prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 78.3 percent
Egger's p-value: 0.164

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

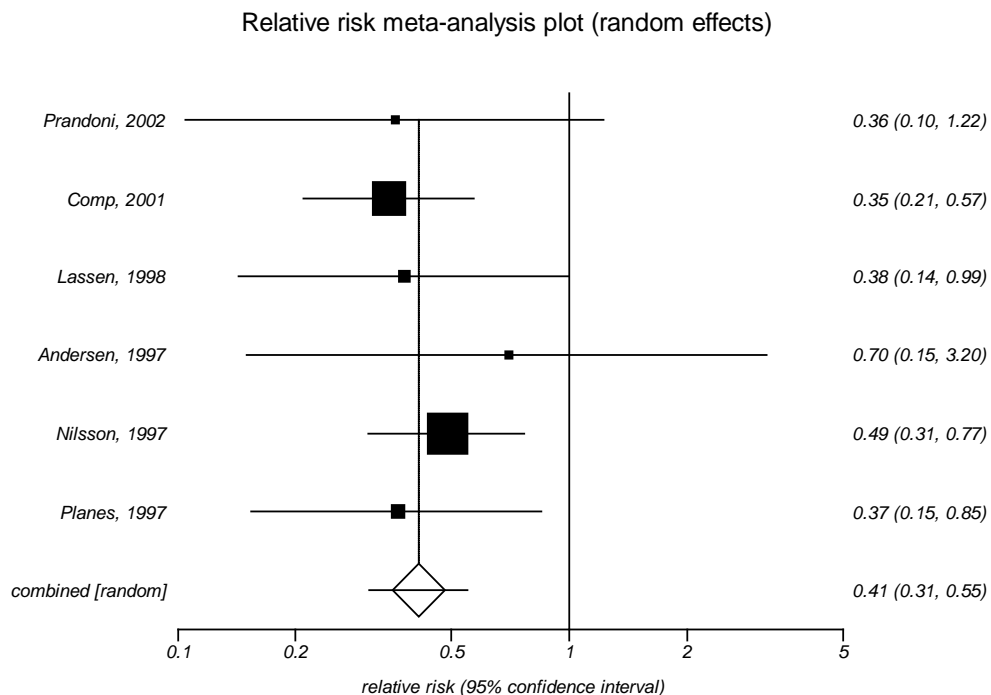
Figure 229. Impact of prolonged prophylaxis versus standard duration of prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 90.9 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

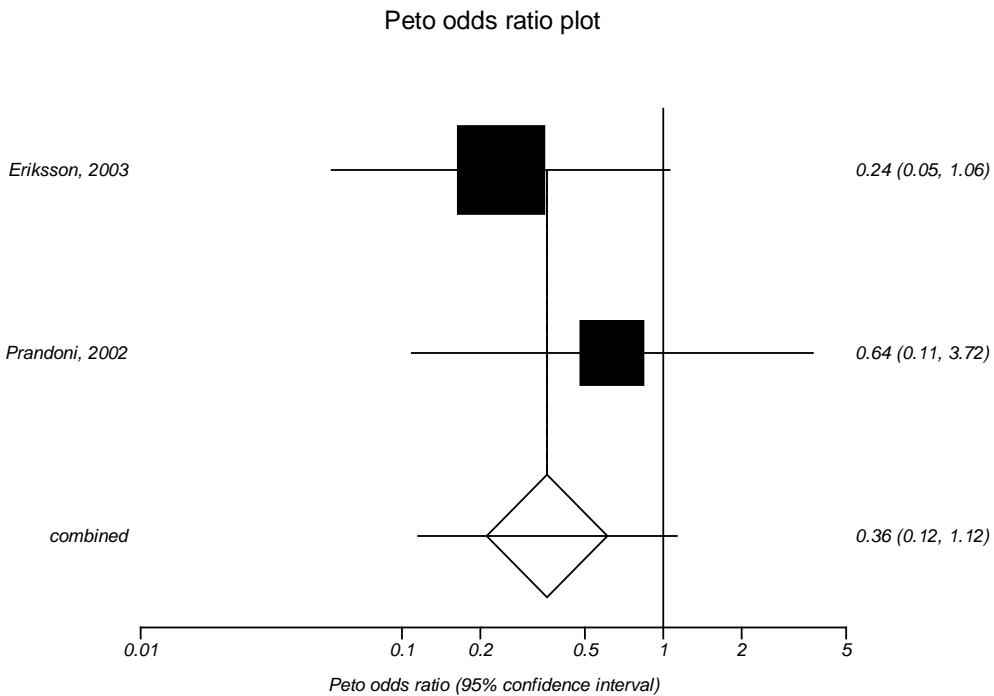
Figure 230. Impact of prolonged prophylaxis versus standard duration of prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

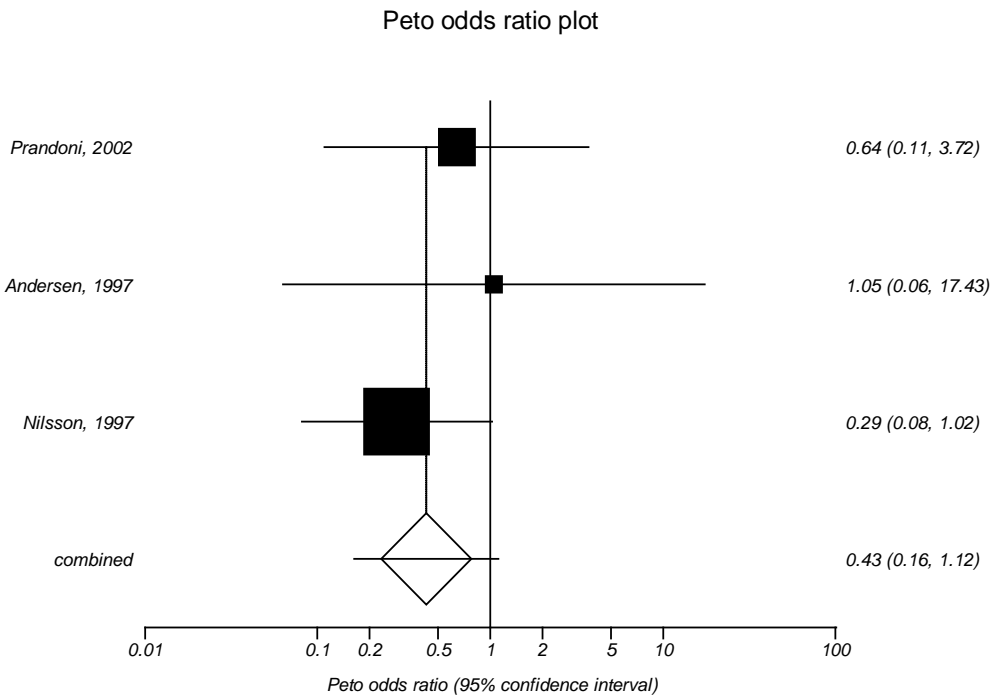
Figure 231. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

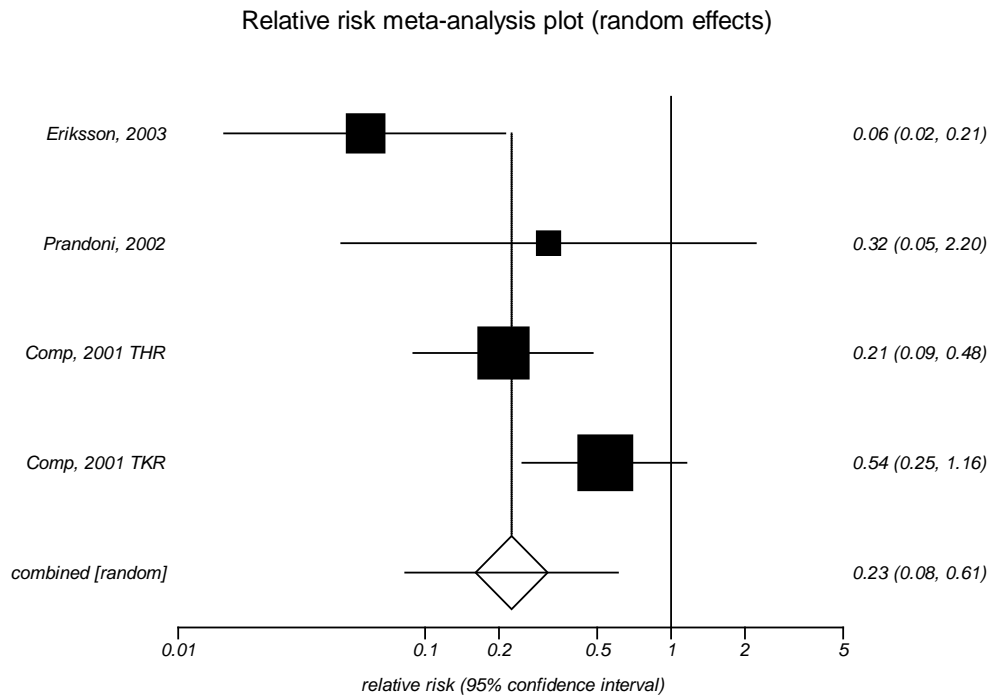
Figure 232. Impact of prolonged prophylaxis versus standard duration of prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

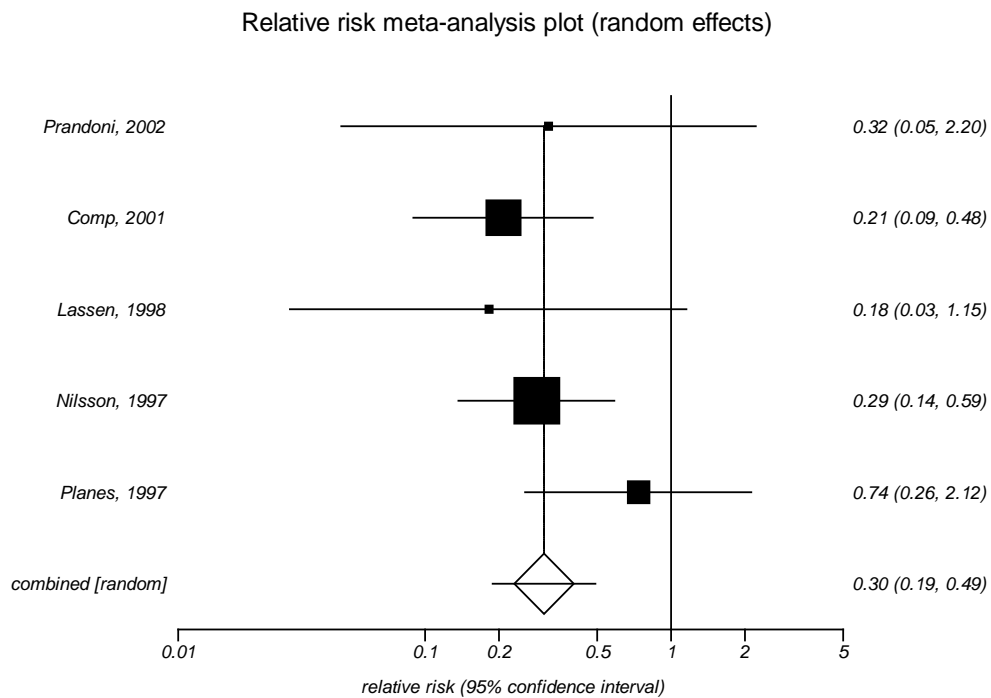
Figure 233. Impact of prolonged prophylaxis versus standard duration of prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 65.5 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

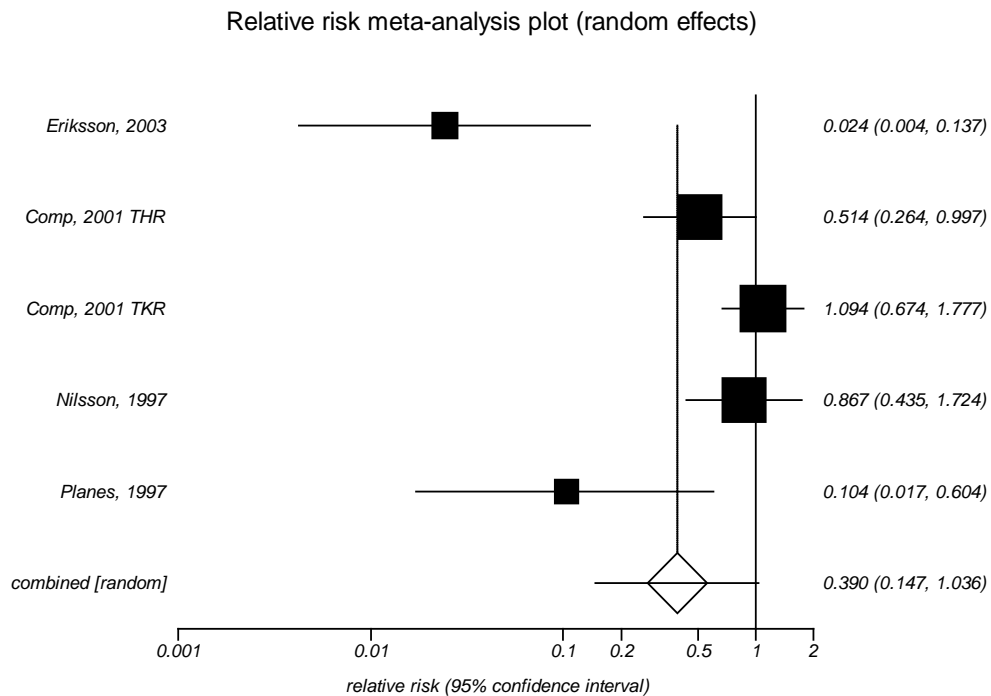
Figure 234. Impact of prolonged prophylaxis versus standard duration of prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery limited total hip replacement surgery



I^2 : 0 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

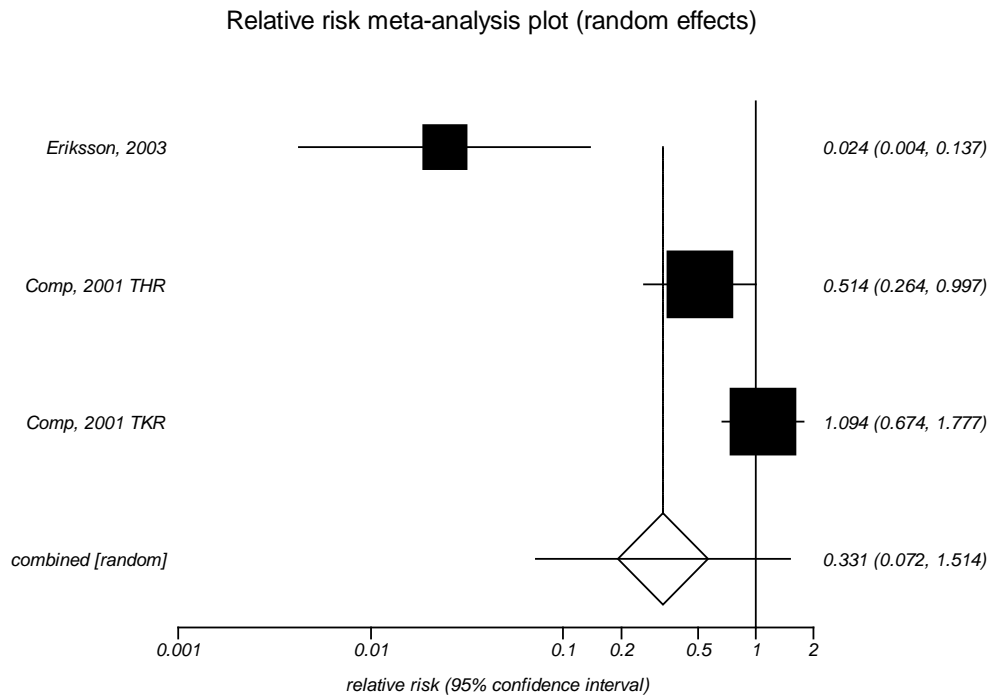
Figure 235. Impact of prolonged prophylaxis versus standard duration of prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery



I^2 : 83.6 percent
Egger's p-value: 0.023

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

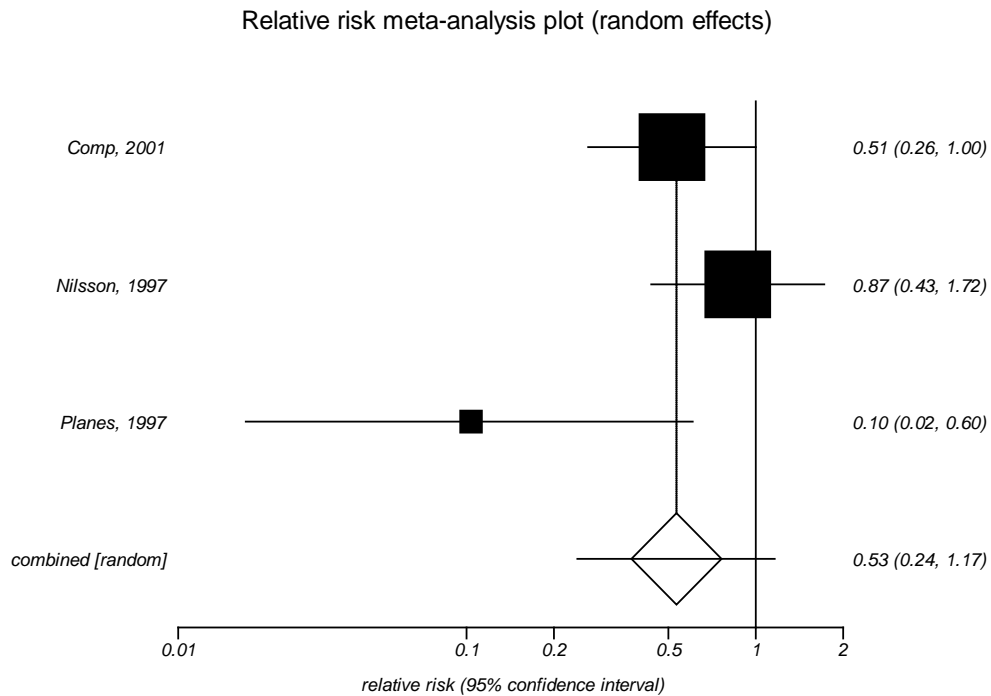
Figure 236. Impact of prolonged prophylaxis versus standard duration of prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 90.3 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

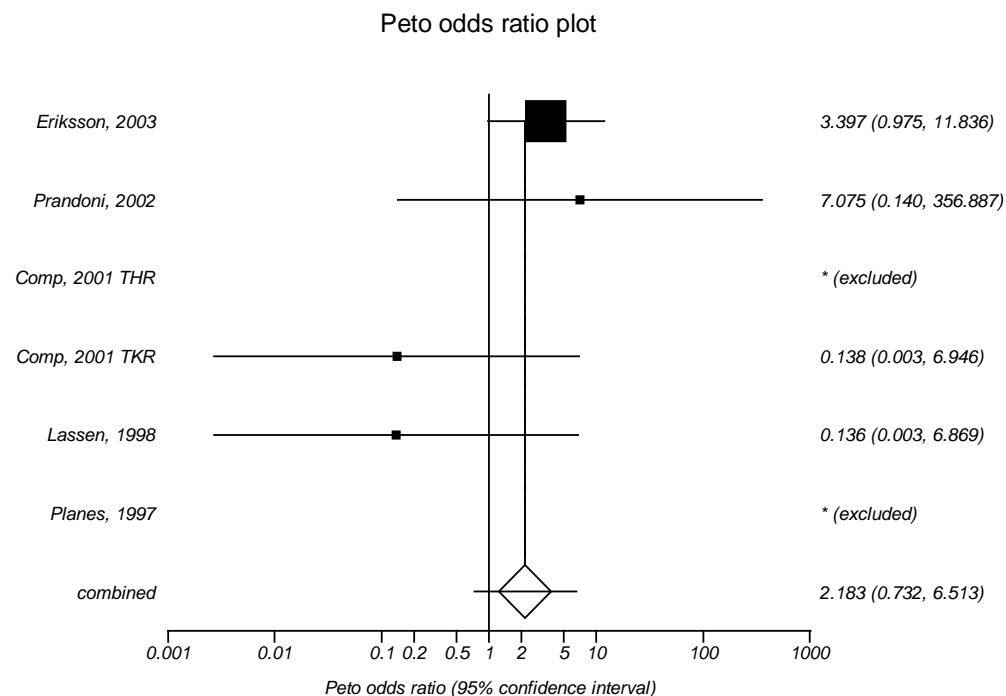
Figure 237. Impact of prolonged prophylaxis versus standard duration of prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : 53.4 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

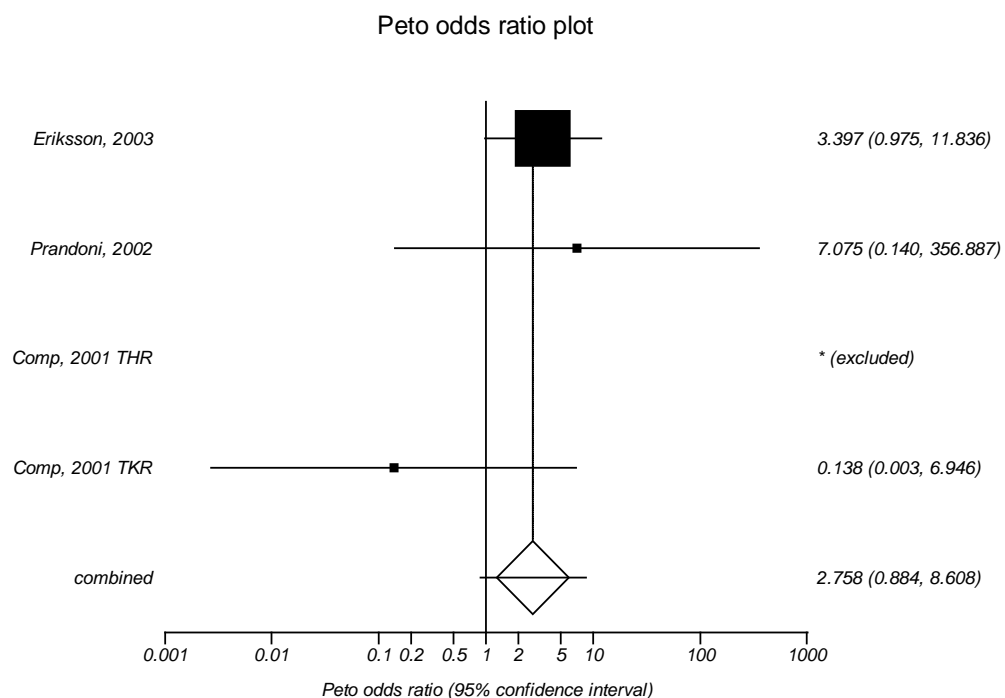
Figure 238. Impact of prolonged prophylaxis versus standard duration of prophylaxis on major bleeding in patients who had major orthopedic surgery



I²: 35.6 percent
Egger's p-value: 0.334

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

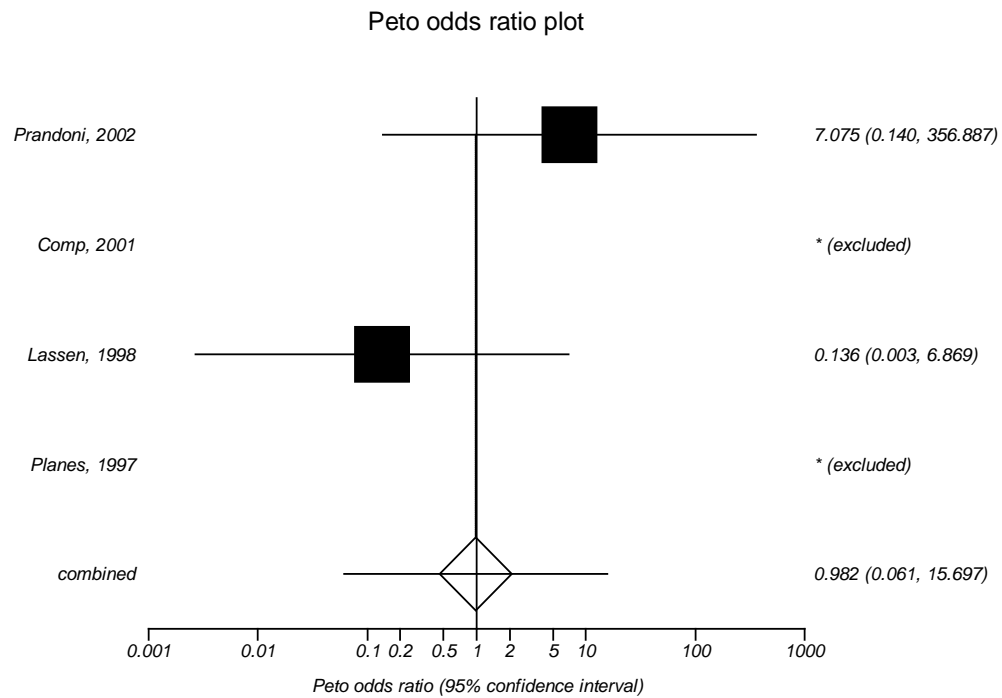
Figure 239. Impact of prolonged prophylaxis versus standard duration of prophylaxis on major bleeding in patients who had major orthopedic surgery limited to trials published from 2001-present



I^2 : 22.3 percent

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

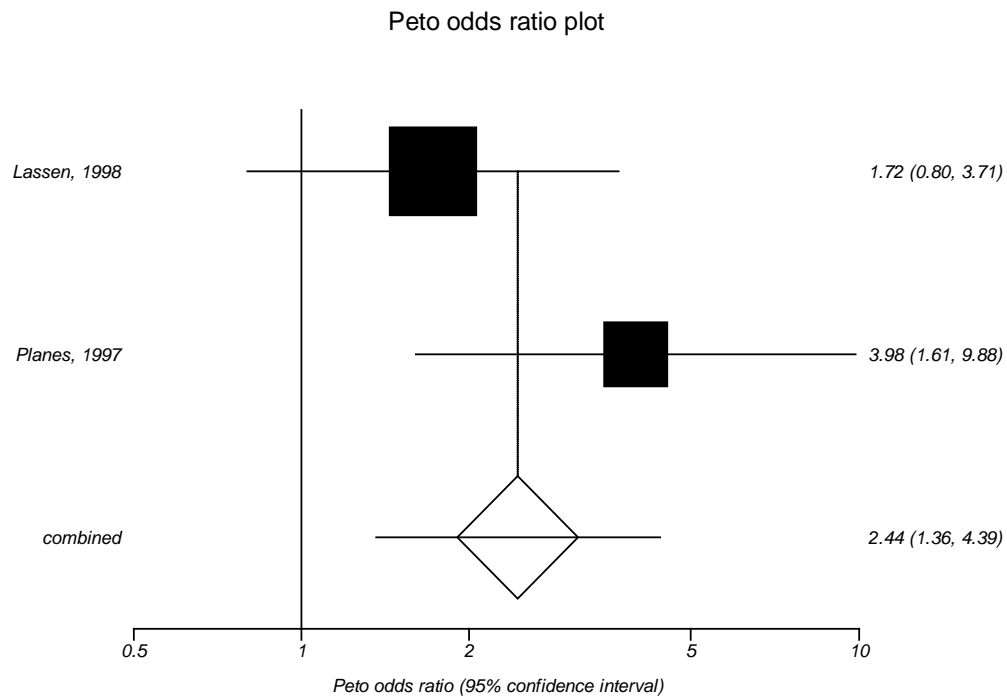
Figure 240. Impact of prolonged prophylaxis versus standard duration of prophylaxis on major bleeding in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

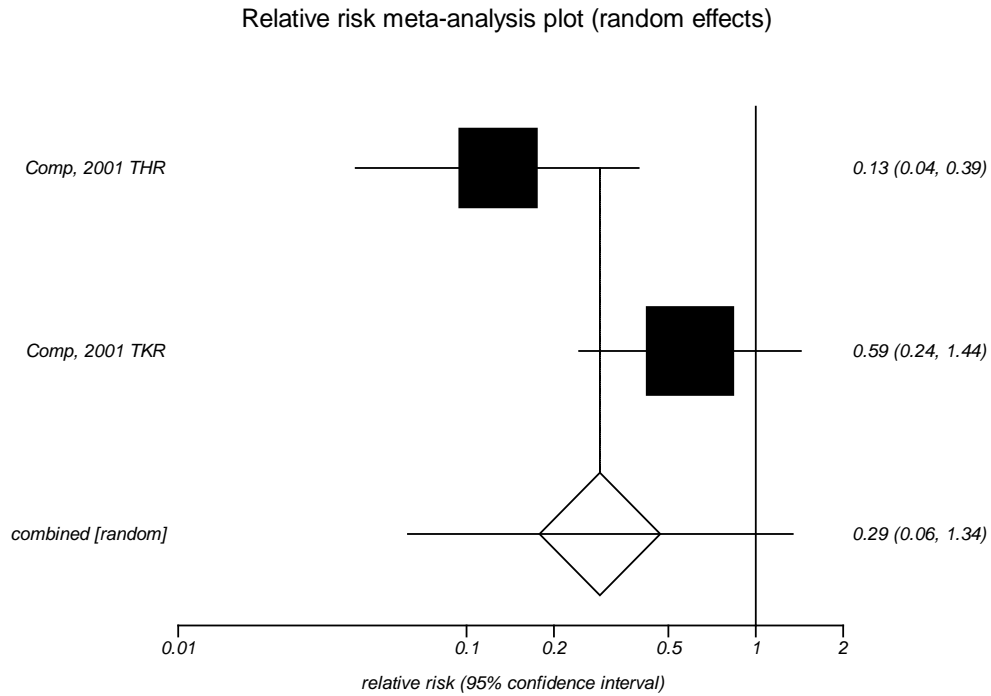
Figure 241. Impact of prolonged prophylaxis versus standard duration of prophylaxis on minor bleeding in patients who had major orthopedic surgery limited to total hip replacement surgery



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 242. Impact of prolonged prophylaxis versus standard duration of prophylaxis on readmission in patients who had major orthopedic surgery (same as limited to trials published from 2001-present)



I^2 : Too few strata

Legend: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Appendix H. Strength of Evidence Rating

Table 24. Strength of evidence for the incidence of final, intermediate and adverse outcomes in total hip replacement surgery

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	5	RCT	Very serious limitation	Very serious inconsistency	No indirectness	Serious imprecision	Low
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Deep vein thrombosis	8	RCT	Very serious limitation	Very serious inconsistency	No indirectness	No imprecision	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	4	RCT	Serious limitation	Very serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	2	RCT	Very serious limitation	Serious inconsistency	No indirectness	Very serious imprecision	Low
Major bleeding	5	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Major bleeding leading to reoperation	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Minor bleeding	5	RCT	Serious limitation	Very serious inconsistency	No indirectness	Serious imprecision	Low
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 25. Strength of evidence for the incidence of final, intermediate and adverse outcomes in total knee replacement surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings Quality
				Consistency	Directness		
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	3 (2,1)	RCT, OBS	Very serious limitation	No inconsistency	No indirectness	No imprecision	Low
Fatal pulmonary embolism	2 (1,1)	RCT, OBS	Very serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	2 (1,1)	RCT, OBS	Very serious limitation	NA	No indirectness	NA	Insufficient
Deep vein thrombosis	4 (2,1)	RCT, OBS	Very serious limitation	Serious inconsistency	No indirectness	Very serious imprecision	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	2	RCT	Very serious limitation	Serious inconsistency	No indirectness	Very serious imprecision	Low
Distal deep vein thrombosis	2	RCT	Very serious limitation	No inconsistency	No indirectness	No imprecision	Low
Major bleeding	2	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Major bleeding leading to reoperation	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Minor bleeding	2	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 26. Strength of evidence for the incidence of final, intermediate and adverse outcomes in hip fracture surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Deep vein thrombosis	1	RCT	Very serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	RCT	Very serious limitation	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 27. Strength of evidence for the impact of spinal versus epidural anesthesia on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 28. Strength of evidence for the impact of general versus regional anesthesia on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	6(4,2)	RCT, OBS	Serious limitation	Serious inconsistency	No indirectness	NA	Low
Asymptomatic deep vein thrombosis	2	RCT	Serious limitation	Serious inconsistency	No indirectness	NA	Insufficient
Symptomatic deep vein thrombosis	2	RCT	Serious limitation	NA	No indirectness	NA	Low
Proximal deep vein thrombosis	5	RCT	Serious limitation	Serious inconsistency	No Indirectness	NA	Low
Distal deep vein thrombosis	4	RCT	Serious limitation	Serious inconsistency	No indirectness	NA	Insufficient
Major bleeding	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 29. Strength of evidence for the impact of cemented versus noncemented arthroplasty on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	5 (2,3)	RCT, OBS	Serious limitation	Serious inconsistency	No indirectness	NA	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No Indirectness	NA	Low
Distal deep vein thrombosis	2	RCT	Serious limitation	Serious inconsistency	No indirectness	NA	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 30. Strength of evidence for the impact of bone vacuum cement versus standard cement on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Major bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 31. Strength of evidence for the impact of tourniquet versus no tourniquet on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	No inconsistency	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Symptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No indirectness	NA	Insufficient
Distal deep vein thrombosis	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 32. Strength of evidence for the impact of tourniquet release prior to wound closure versus tourniquet release after wound closure on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Very serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 33. Strength of evidence for the impact of modified position to maintain femoral blood flow versus standard figure four position on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	RCT	Serious limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 34. Strength of evidence for the impact of minimum hyperflexed knee versus standard hyperflexed knee on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Very serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	Very serious limitation	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 35. Strength of evidence for the impact of tissue fibrin adhesive versus no adhesive on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Symptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 36. Strength of evidence for the impact of primary versus revision surgery on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational ; VTE=venous thromboembolism

Table 37. Strength of evidence for the impact of perioperative blood loss on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings
				Consistency	Directness	Precision	Quality
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational ; VTE=venous thromboembolism

Table 38. Strength of evidence for the impact of operative time on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 39. Strength of evidence for the impact of blood transfusions on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings
				Consistency	Directness		Quality
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational ; VTE=venous thromboembolism

Table 40. Strength of evidence for the impact of congestive heart failure on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings
				Consistency	Directness	Precision	Quality
Symptomatic objectively confirmed VTE	2	OBS	No limitations	No inconsistency	No indirectness	NA	Moderate
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational ; VTE=venous thromboembolism

Table 41. Strength of evidence for the impact of inactive malignancy on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational ; VTE=venous thromboembolism

Table 42. Strength of evidence for the impact of hormone replacement therapy on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 43. Strength of evidence for the impact of age on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	2	OBS	Serious limitation	No inconsistency	No indirectness	NA	Low
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	3	OBS	Serious limitation	Serious inconsistency	No indirectness	NA	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	2	OBS	Very serious limitation	No inconsistency	No indirectness	NA	Low
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 44. Strength of evidence for the impact of living at home on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 45. Strength of evidence for the impact of intertrochanteric fractures on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 46. Strength of evidence for the impact of subtrochanteric fractures on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 47. Strength of evidence for the impact of increased hemoglobin on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 48. Strength of evidence for the impact of gender on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	2	OBS	No limitations	Serious inconsistency	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 49. Strength of evidence for the impact of history of venous thromboembolism on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 50. Strength of evidence for the impact of varicose veins on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 51. Strength of evidence for the impact of genitourinary infection on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 52. Strength of evidence for the impact of cardiovascular disease on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings
				Consistency	Directness		Quality
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 53. Strength of evidence for the impact of thyroid hormone replacement on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 54. Strength of evidence for the impact of phlebitis on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 55. Strength of evidence for the impact of peripheral vascular disease on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 56. Strength of evidence for the impact of weight on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	3	OBS	Very serious limitations	Serious inconsistency	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 57. Strength of evidence for the impact of smoking on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 58. Strength of evidence for the impact of height on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 59. Strength of evidence for the impact of factor V Leiden mutation on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings
				Consistency	Directness	Precision	Quality
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 60. Strength of evidence for the impact of blood disorders on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 61. Strength of evidence for the impact of metabolic syndrome on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 62. Strength of evidence for the impact of education on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 63. Strength of evidence for the impact of diabetes mellitus on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 64. Strength of evidence for the impact of hypertension on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 65. Strength of evidence for the impact of hyperlipidemia on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings Quality
				Consistency	Directness		
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 66. Strength of evidence for the impact of comorbidities on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	OBS	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 67. Strength of evidence for the impact of risk of bleeding on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 68. Strength of evidence for the impact of surgical procedure on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings
				Consistency	Directness	Precision	Quality
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 69. Strength of evidence for the impact of type of prophylaxis on the risk of venous thromboembolic or bleeding outcomes.

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings Quality
				Consistency	Directness		
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Very serious limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 70. Strength of evidence for the causal link between deep vein thrombosis and pulmonary embolism in major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment	Precision	Summary of Findings Quality
				Consistency	Directness		
Symptomatic objectively confirmed VTE	11 (9,2)	RCT, OBS	Serious risk of bias	Serious inconsistency	Indirectness	NA	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 71. Strength of evidence for final, intermediate and adverse outcomes comparing pharmacologic prophylaxis to no prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Major VTE	1	RCT	No limitations	Serious limitation	No indirectness	Serious imprecision	Low
Pulmonary Embolism	12	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Low
Fatal pulmonary embolism	7 (6,1)	RCT, OBS	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Nonfatal pulmonary embolism	7 (6,1)	RCT, OBS	No limitations	No serious inconsistency	No indirectness	Very serious imprecision	Low
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	13 (10, 3)	RCT , OBS	No limitations	No serious inconsistency	No indirectness	Serious imprecision	Moderate
Mortality due to bleeding	10 (9,1)	RCT, OBS	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	17	RCT	Serious limitations	Serious inconsistency	No indirectness	No imprecision	Moderate
Asymptomatic deep vein thrombosis	3	RCT	No limitations	No inconsistency	No indirectness	No imprecision	Moderate
Symptomatic deep vein thrombosis	5 (4,1)	RCT, OBS	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Proximal deep vein thrombosis	12	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Distal deep vein thrombosis	7	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Major bleeding	9 (8,1)	RCT, OBS	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Major bleeding leading to reoperation	2	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Minor bleeding	6	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Surgical site bleeding	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	1	OBS	Serious risk of bias	NA	No indirectness	NA	Insufficient
Reoperation	1	OBS	Serious risk of bias	NA	No indirectness	NA	Insufficient

Abbreviations: NA=not applicable; RCT= randomized controlled trial; OBS=observational; VTE=venous thromboembolism

Table 72. Strength of evidence for final, intermediate and adverse outcomes comparing mechanical prophylaxis to no prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Nonfatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No limitation	NA	No indirectness	No imprecision	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	No limitation	NA	No indirectness	Serious imprecision	Insufficient
Distal deep vein thrombosis	1	RCT	No limitation	NA	No indirectness	Serious imprecision	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 73. Strength of evidence for final, intermediate and adverse outcomes comparing oral antiplatelet agents prophylaxis to oral vitamin K antagonists prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Fatal pulmonary embolism	2 (1,1)	RCT, OBS	No limitations	NA	No indirectness	Very serious imprecision	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Nonfatal pulmonary embolism	2 (1,1)	RCT, OBS	No limitations	NA	No indirectness	NA	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	3 (1, 2)	RCT, OBS	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	1	OBS	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT: randomized controlled trial; OBS=observational; VTE=venous thromboembolism

Table 74. Strength of evidence for final, intermediate and adverse outcomes comparing oral antiplatelet agents prophylaxis to mechanical prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality			Assessment	Summary of Findings Quality
				Consistency	Directness	Precision		
Symptomatic objectively confirmed VTE	0	---	---	---	---	---		Insufficient
Major VTE	0	---	---	---	---	---		Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision		Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---		Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---		Insufficient
Post thrombotic syndrome	0	---	---	---	---	---		Insufficient
Mortality	0	---	---	---	---	---		Insufficient
Mortality due to bleeding	0	---	---	---	---	---		Insufficient
Health related quality of life	0	---	---	---	---	---		Insufficient
Deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision		Moderate
Asymptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision		Insufficient
Symptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision		Insufficient
Proximal deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision		Insufficient
Distal deep vein thrombosis	1	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision		Insufficient
Major bleeding	0	---	---	---	---	---		Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---		Insufficient
Minor bleeding	0	---	---	---	---	---		Insufficient
Surgical site bleeding	0	---	---	---	---	---		Insufficient
Bleeding leading to infection	0	---	---	---	---	---		Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---		Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---		Insufficient
Discomfort	0	---	---	---	---	---		Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 75. Strength of evidence for final, intermediate and adverse outcomes comparing injectable low molecular weight heparin prophylaxis to injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	10	RCT	No limitations	Serious inconsistency	No indirectness	No imprecision	Moderate
Fatal pulmonary embolism	10	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Nonfatal pulmonary embolism	10	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	8	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Mortality due to bleeding	7	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	14	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Asymptomatic deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Low
Symptomatic deep vein thrombosis	3	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Proximal deep vein thrombosis	9	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Distal deep vein thrombosis	8	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Major bleeding	7	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Major bleeding leading to reoperation	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Minor bleeding	5	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Surgical site bleeding	3	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	3	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	2	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT= randomized controlled trial; VTE=venous thromboembolism

Table 76. Strength of evidence for final, intermediate and adverse outcomes comparing injectable low molecular weight heparin prophylaxis to injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	5	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Low
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	2	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Fatal pulmonary embolism	5	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Low
Nonfatal pulmonary embolism	5	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Mortality	7 (5, 2)	RCT, OBS	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Mortality due to bleeding	6 (5,1)	RCT, OBS	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	5	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	6	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Proximal deep vein thrombosis	5	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	5	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Major bleeding	7 (5,2)	RCT, OBS	No limitations	Serious inconsistency	No indirectness	No imprecision	Moderate
Major bleeding leading to reoperation	4	RCT	No limitation	No inconsistency	No indirectness	Serious imprecision	Moderate
Minor bleeding	2	RCT	Serious limitations	No inconsistency	No indirectness	Serious imprecision	Low
Surgical site bleeding	1	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 77. Strength of evidence for final, intermediate and adverse outcomes comparing injectable low molecular weight heparin prophylaxis to injectable or oral direct thrombin inhibitors prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Pulmonary Embolism	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Fatal pulmonary embolism	3	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Low
Nonfatal pulmonary embolism	2	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	5	RCT	No limitation	No inconsistency	No indirectness	Serious imprecision	Moderate
Mortality due to bleeding	3	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	No imprecision	Insufficient
Asymptomatic deep vein thrombosis	2	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Symptomatic deep vein thrombosis	4	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Proximal deep vein thrombosis	3	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	1	RCT	No limitations	No inconsistency	No indirectness	No imprecision	Insufficient
Major bleeding	4	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Major bleeding leading to reoperation	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Minor bleeding	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Surgical site bleeding	1	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality		Assessment		Summary of Findings Quality
				Consistency		Directness	Precision	
Bleeding leading to infection	0	---	---	---		---	---	Insufficient
Bleeding leading to transfusion	2	RCT	No limitations	No inconsistency		No indirectness	No imprecision	High
Heparin-induced thrombocytopenia	0	---	---	---		---	---	Insufficient
Discomfort	0	---	---	---		---	---	Insufficient
Readmission	0	---	---	---		---	---	Insufficient
Reoperation	0	---	---	---		---	---	Insufficient

Abbreviations: NA=not applicable; RCT: randomized controlled trial; VTE=venous thromboembolism

Table 78. Strength of evidence for final, intermediate and adverse outcomes comparing injectable low molecular weight heparin prophylaxis to oral vitamin K antagonists prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality		Assessment		Summary of Findings Quality
				Consistency		Directness	Precision	
Symptomatic objectively confirmed VTE	2	RCT	No limitations	Serious inconsistency		No indirectness	Serious imprecision	Low
Major VTE	0	---	---	---		---	---	Insufficient
Pulmonary Embolism	5	RCT	No limitations	No inconsistency		No indirectness	Serious imprecision	Moderate
Fatal pulmonary embolism	4	RCT	Serious limitation	NA		No indirectness	Very serious imprecision	Insufficient
Nonfatal pulmonary embolism	3	RCT	No limitations	Serious inconsistency		No indirectness	Serious imprecision	Low
Post thrombotic syndrome	0	---	---	---		---	---	Insufficient
Mortality	6	RCT	No limitations	No inconsistency		No indirectness	Serious imprecision	Moderate
Mortality due to bleeding	4	RCT	Serious limitation	NA		No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---		---	---	Insufficient
Deep vein thrombosis	5	RCT	Serious limitation	Serious inconsistency		No indirectness	No imprecision	Low

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Asymptomatic deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	No imprecision	Insufficient
Symptomatic deep vein thrombosis	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Proximal deep vein thrombosis	6	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Major bleeding	7	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Major bleeding leading to reoperation	2	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Minor bleeding	8	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Surgical site bleeding	2	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Heparin-induced thrombocytopenia	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	2	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 79. Strength of evidence for final, intermediate and adverse outcomes comparing injectable low molecular weight heparin prophylaxis to mechanical prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality			Assessment		Summary of Findings Quality
				Consistency	Directness	Precision			
Symptomatic objectively confirmed VTE	0	---	---	---	---	---			Insufficient
Major VTE	0	---	---	---	---	---			Insufficient
Pulmonary Embolism	1	RCT	No limitations	NA	No indirectness	Very serious imprecision			Insufficient
Fatal pulmonary embolism	2	RCT	No limitations	NA	No indirectness	Serious imprecision			Insufficient
Nonfatal pulmonary embolism	1	RCT	No limitations	NA	No indirectness	Very serious imprecision			Insufficient
Post thrombotic syndrome	0	---	---	---	---	---			Insufficient
Mortality	2	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision			Low
Mortality due to bleeding	2	RCT	No limitations	NA	No indirectness	Very serious imprecision			Insufficient
Health related quality of life	0	---	---	---	---	---			Insufficient
Deep vein thrombosis	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision			Moderate
Asymptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision			Insufficient
Symptomatic deep vein thrombosis	2	RCT	No limitation	NA	No indirectness	Very serious imprecision			Insufficient
Proximal deep vein thrombosis	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision			Moderate
Distal deep vein thrombosis	3	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision			Moderate
Major bleeding	0	---	---	---	---	---			Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---			Insufficient
Minor bleeding	0	---	---	---	---	---			Insufficient
Surgical site bleeding	0	---	---	---	---	---			Insufficient
Bleeding leading to infection	0	---	---	---	---	---			Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality		Assessment		Summary of Findings Quality
				Consistency		Directness	Precision	
Bleeding leading to transfusion	0	---	---	---		---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---		---	---	Insufficient
Discomfort	1	RCT	No limitations	NA		No indirectness	No imprecision	Insufficient
Readmission	2	RCT	No limitations	No inconsistency		No indirectness	Serious imprecision	Low
Reoperation	0	---	---	---		---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 80. Strength of evidence for final, intermediate and adverse outcomes comparing injectable unfractionated heparin prophylaxis to injectable or oral direct thrombin inhibitors prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality		Assessment		Summary of Findings Quality
				Consistency		Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---		---	---	Insufficient
Major VTE	0	---	---	---		---	---	Insufficient
Pulmonary Embolism	2	RCT	No limitations	Serious inconsistency		No indirectness	Very serious imprecision	Low
Fatal pulmonary embolism	2	RCT	No limitations	NA		No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	2	RCT	No limitations	Serious inconsistency		No indirectness	Very serious imprecision	Low
Post thrombotic syndrome	0	---	---	---		---	---	Insufficient
Mortality	2	RCT	No limitations	No inconsistency		No indirectness	Very serious imprecision	Low
Mortality due to bleeding	2	RCT	No limitations	NA		No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---		---	---	Insufficient
Deep vein thrombosis	2	RCT	No limitations	No inconsistency		No indirectness	Serious imprecision	Moderate
Asymptomatic deep vein thrombosis	0	---	---	---		---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	2	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	2	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Low
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 81. Strength of evidence for final, intermediate and adverse outcomes comparing injectable unfractionated heparin prophylaxis to injectable or oral factor Xa inhibitors prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	OBS	Serious limitation	NA	No indirectness	NA	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	1	OBS	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 82. Strength of evidence for final, intermediate and adverse outcomes comparing injectable unfractionated heparin prophylaxis to mechanical prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	No imprecision	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 83. Strength of evidence for final, intermediate and adverse outcomes comparing oral vitamin K antagonists prophylaxis to mechanical prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	2	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	3	RCT	Serious limitation	Serious inconsistency	No indirectness	Serious imprecision	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	3	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Distal deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Very serious imprecision	Insufficient
Major bleeding	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Major bleeding leading to reoperation	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Minor bleeding	2	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT: randomized controlled trial; VTE=venous thromboembolism

Table 84. Strength of evidence for final, intermediate and adverse outcomes comparing enoxaparin prophylaxis to other low molecular weight heparin agents in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	2	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Nonfatal pulmonary embolism	2	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	2	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Asymptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Symptomatic deep vein thrombosis	2	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Proximal deep vein thrombosis	2	RCT	No limitations	Serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	No imprecision	Insufficient
Major bleeding	2	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Moderate
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	1	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Surgical site bleeding	2	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Low
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Heparin-induced thrombocytopenia	1	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 85 . Strength of evidence for final, intermediate and adverse outcomes comparing the intermittent pneumatic compression device by Kendall to the Venaflow intermittent pneumatic compression device in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality Assessment			Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Fatal pulmonary embolism	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Nonfatal pulmonary embolism	1	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Distal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 86. Strength of evidence for final, intermediate and adverse outcomes comparing the ActiveCare intermittent pneumatic compression device to the Flowtron intermittent pneumatic compression device in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Mortality due to bleeding	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	OBS	Serious limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; OBS=observational; VTE=venous thromboembolism

Table 87. Strength of evidence for final, intermediate and adverse outcomes comparing intermittent pneumatic compression versus graduated compression stockings in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	2	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	No imprecision	Low
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	1	RCT	Serious limitation	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	2	RCT	Serious limitation	No inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	1	RCT	No limitations	No inconsistency	No indirectness	No imprecision	Low
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 88. Strength of evidence for final, intermediate and adverse outcomes comparing pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	2	RCT	No limitations	No serious inconsistency	No indirectness	Very serious imprecision	Low
Fatal pulmonary embolism	2	RCT	No limitations	NA	No indirectness	NA	Insufficient
Nonfatal pulmonary embolism	2	RCT	No limitations	No serious inconsistency	No indirectness	Very serious imprecision	Low
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	3	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	3	RCT	No limitations	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	4	RCT	No limitations	No serious inconsistency	No indirectness	No imprecision	Moderate
Asymptomatic deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Symptomatic deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Proximal deep vein thrombosis	5	RCT	No limitations	No serious inconsistency	No indirectness	Very serious imprecision	Low
Distal deep vein thrombosis	3	RCT	No limitations	No serious inconsistency	No indirectness	Serious imprecision	Moderate
Major bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 89. Strength of evidence for final, intermediate and adverse outcomes comparing pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious limitations	NA	No indirectness	Very serious imprecision	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Mortality due to bleeding	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Symptomatic deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient
Proximal deep vein thrombosis	2	RCT	Serious limitation	No serious inconsistency	No indirectness	Serious imprecision	Low
Distal deep vein thrombosis	1	RCT	No limitations	NA	No indirectness	NA	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 90. Strength of evidence for final, intermediate and adverse outcomes comparing extended duration prophylaxis versus standard duration prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	4	RCT	No limitations	Serious inconsistency	No indirectness	No imprecision	Moderate
Major VTE	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient
Pulmonary Embolism	7	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Fatal pulmonary embolism	6	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Nonfatal pulmonary embolism	6	RCT	Serious limitation	No inconsistency	No indirectness	No imprecision	Moderate
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	6	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Mortality due to bleeding	5	RCT	No limitations	NA	No indirectness	NA	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	8	RCT	No limitations	Serious inconsistency	No indirectness	No imprecision	Moderate
Asymptomatic deep vein thrombosis	4	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Symptomatic deep vein thrombosis	5	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Proximal deep vein thrombosis	7	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Distal deep vein thrombosis	4	RCT	Serious limitation	Serious inconsistency	No indirectness	Serious imprecision	Low
Major bleeding	5	RCT	No limitations	No inconsistency	No indirectness	Very serious imprecision	Low
Major bleeding leading to reoperation	1	RCT	No limitations	NA	No indirectness	Very serious imprecision	Insufficient
Minor bleeding	3	RCT	No limitations	No inconsistency	No indirectness	No imprecision	High
Surgical site bleeding	1	RCT	No limitations	NA	No indirectness	No imprecision	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	2	RCT	No limitations	NA	No indirectness	Serious imprecision	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	1	RCT	No limitations	No inconsistency	No indirectness	Serious imprecision	Low
Reoperation	1	RCT	Serious limitation	NA	No indirectness	Serious imprecision	Insufficient

Abbreviations: NA=not applicable; RCT=randomized controlled trial; VTE=venous thromboembolism

Table 91. Strength of evidence for final, intermediate and adverse outcomes comparing inferior vena cava filters to mechanical prophylaxis in patients who had major orthopedic surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major VTE	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Nonfatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: VTE=venous thromboembolism

Table 92. Strength of evidence for final, intermediate and adverse outcomes comparing prophylaxis versus no prophylaxis in patients who had knee arthroscopy

Outcome	Number of studies	Design	Risk of Bias	Quality		Assessment		Summary of Findings Quality
				Consistency		Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---		---	---	Insufficient
Major venous thromboembolism	0	---	---	---		---	---	Insufficient
Pulmonary Embolism	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---		---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---		---	---	Insufficient
Post thrombotic syndrome	0	---	---	---		---	---	Insufficient
Mortality	0	---	---	---		---	---	Insufficient
Mortality due to bleeding	0	---	---	---		---	---	Insufficient
Health related quality of life	0	---	---	---		---	---	Insufficient
Deep vein thrombosis	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---		---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---		---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Distal deep vein thrombosis	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Major bleeding	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---		---	---	Insufficient
Minor bleeding	1	RCT	Serious risk of bias	NA		No indirectness	NA	Insufficient
Surgical site bleeding	0	---	---	---		---	---	Insufficient
Bleeding leading to infection	0	---	---	---		---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---		---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 93. Strength of evidence for final, intermediate and adverse outcomes comparing prophylaxis versus no prophylaxis in patients who had surgical repair of a lower extremity injury distal to the hip

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	1	RCT	No risk of bias	NA	No indirectness	NA	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	1	RCT	No risk of bias	NA	No indirectness	NA	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	1	RCT	No risk of bias	NA	No indirectness	NA	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Major bleeding	1	RCT	No risk of bias	NA	No indirectness	NA	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 94. Strength of evidence for final, intermediate and adverse outcomes comparing prophylaxis versus no prophylaxis in patients who had elective spine surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 95. Strength of evidence for final, intermediate and adverse outcomes comparing injectable pharmacologic prophylaxis versus mechanical prophylaxis in patients who had knee arthroscopy

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 96. Strength of evidence for final, intermediate and adverse outcomes comparing injectable pharmacologic prophylaxis versus mechanical prophylaxis in patients who had surgical repair of a lower extremity injury distal to the hip

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Table 97. Strength of evidence for final, intermediate and adverse outcomes comparing injectable pharmacologic prophylaxis versus mechanical prophylaxis in patients who had elective spine surgery

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Symptomatic objectively confirmed VTE	0	---	---	---	---	---	Insufficient
Major venous thromboembolism	0	---	---	---	---	---	Insufficient
Pulmonary Embolism	0	---	---	---	---	---	Insufficient
Fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Non-fatal pulmonary embolism	0	---	---	---	---	---	Insufficient
Post thrombotic syndrome	0	---	---	---	---	---	Insufficient
Mortality	0	---	---	---	---	---	Insufficient
Mortality due to bleeding	0	---	---	---	---	---	Insufficient
Health related quality of life	0	---	---	---	---	---	Insufficient

Outcome	Number of studies	Design	Risk of Bias	Quality	Assessment		Summary of Findings Quality
				Consistency	Directness	Precision	
Deep vein thrombosis	0	---	---	---	---	---	Insufficient
Asymptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Symptomatic deep vein thrombosis	0	---	---	---	---	---	Insufficient
Proximal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Distal deep vein thrombosis	0	---	---	---	---	---	Insufficient
Major bleeding	0	---	---	---	---	---	Insufficient
Major bleeding leading to reoperation	0	---	---	---	---	---	Insufficient
Minor bleeding	0	---	---	---	---	---	Insufficient
Surgical site bleeding	0	---	---	---	---	---	Insufficient
Bleeding leading to infection	0	---	---	---	---	---	Insufficient
Bleeding leading to transfusion	0	---	---	---	---	---	Insufficient
Heparin-induced thrombocytopenia	0	---	---	---	---	---	Insufficient
Discomfort	0	---	---	---	---	---	Insufficient
Readmission	0	---	---	---	---	---	Insufficient
Reoperation	0	---	---	---	---	---	Insufficient

Abbreviations: RCT: randomized controlled trial; VTE=venous thromboembolism

Appendix I. Applicability Rating for Individual Trials and Studies and the Body of Evidence

Table 98. Evaluation of applicability for individual randomized controlled trials

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Yokote, 2011	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Assessed final health outcomes 2. Used intention-to-treat analysis 3. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:81.6%, M:18.4%) • Only patients undergoing THA • Primary THA only • Conducted in Japan • Did not report adverse events • Duration of followup for some final health outcomes (11 days)
Fuji, 2010	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ration (F:84%, M:16%) • Only patients undergoing TKA • Conducted in Japan • Duration of followup for final and intermediate health outcomes (postoperative) • Only primary surgery
Chin, 2009	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:92%, M:8%) • Only patients undergoing TKR • Conducted in Singapore • Duration of followup for final and intermediate health outcomes (postoperative) • Primary or revision surgery not reported

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Ginsberg, 2009	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing TKA Only primary surgery Duration of followup for final and intermediate health outcomes (postoperative) Conducted in 4 countries including USA
Edwards, 2008	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Outcomes	<ul style="list-style-type: none"> Primary or revision surgery not reported DVT outcomes and mortality assessed postoperatively Did not report adverse outcomes
Fuji, 2008 THA	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F:87%, M:13 %) Only patients undergoing THA Conducted in Japan Duration of followup for final and intermediate health outcomes (postoperative) Only primary surgery
Fuji, 2008 TKA	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F:87%, M:13 %) Only patients undergoing TKA Conducted in Japan Duration of followup for final and intermediate health outcomes (postoperative) Only primary surgery

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Thorey, 2008	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Used intention-to-treat analysis 3. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Primary or revision surgery not reported • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=20) • Conducted in Germany
Eriksson, 2007a	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery • Did not use intention-to-treat analysis • Duration of followup for final and intermediate health outcomes (postoperative) • Conducted in 105 centers not including USA
Eriksson, 2007b	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Only primary surgery • Duration of followup for final and intermediate health outcomes (postoperative) • Conducted in 115 centers not including USA
Lassen, 2007	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKR • Primary or revision surgery not reported • Duration of followup for final and intermediate health outcomes (postoperative) • Conducted in 97 centers including USA

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Bonneux, 2006	Study Designation: Efficacy Study Composite Score: 1 of 7	1. Assessed adverse outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:79%; M:21%) • Only patients undergoing TKA • Mainly primary surgery (revision surgery:5%) • Did not assess final health outcomes • Did not use intention-to-treat analysis • Small sample size (N=120) • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Belgium
Westrich, 2006	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Used intention-to-treat analysis 3. Adequate sample size 4. Adequate study duration with clinically relevant treatment	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=118) • Duration of followup for intermediate health outcomes (post-operative)
Kalodiki, 1996	Study Designation: Efficacy Study Composite Score: 1 of 7	1. Enrolled primary care population	Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Geographical location not reported • Only primary surgery (100%) • Small sample size (N=78) • Did not use intention -to- treat analysis • Did not report final health outcomes • Did not report adverse outcomes • Duration of followup for intermediate health outcomes (post-operative)

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Senaran, 2006	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Mean age 53.8 years • High female to male ratio (F:71%; M:29%) • Only patients undergoing THA • Primary or revision surgery not reported • Small sample size (N=100) • Duration of followup for final and intermediate health outcomes (42d or until discharge) • Conducted in Turkey
Eriksson, 2005	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Intervention, Outcomes, Setting	<ul style="list-style-type: none"> • Only primary surgery • Duration of followup for final and intermediate health outcomes (post-operative or 30d-42d) • Did not use any of the doses included in Phase 3 trials • Conducted in 60 centers not including USA
Farag, 2005	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis 4. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Primary or revision surgery not reported • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=38) • Duration of followup for intermediate health outcomes (10d)
Lachiewicz, 2004	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKA • Duration of followup for final and intermediate health outcomes (post-operative) • Did not report adverse outcomes

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Silbersack, 2004	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Outcomes, Setting	<ul style="list-style-type: none"> Only primary surgery Duration of followup for final and intermediate health outcomes (post-operative) Did not report adverse outcomes Conducted in Germany
Eriksson, 2003	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F:71%; M:29%) Only patients undergoing HFS Primary or revision surgery not reported Duration of followup for final health outcomes (32d) Conducted in Europe and South America
Kim, 2003	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> Mean age 54.9 yrs Only patients undergoing THR Primary or revision surgery not reported Did not assess adverse outcomes Duration of followup for final and intermediate health outcomes (7d) Conducted in Korea
Lassen, 2002	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Mainly primary surgery (revision:12%) Did not use intention-to-treat analysis Duration of followup for final and intermediate health outcomes (49d) Conducted in 73 centers not including USA
Pitto, 2002	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing TKA Only primary surgery Did not assess adverse outcomes Small sample size (N=130) Duration of followup for final health outcomes (45d) Conducted in Germany

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Prandoni, 2002	Study Designation: Effectiveness Study Composite Score: 7 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Used intention-to-treat analysis 6. Adequate sample size 7. Adequate study duration with clinically relevant treatment 	Population, Setting	<ul style="list-style-type: none"> • Only patients undergoing THA • Primary or revision surgery not reported • Duration of followup for final health outcomes (28d, 90d) • Conducted in Italy
Turpie, 2002	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 	Population, Outcomes Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Duration of followup for final and intermediate health outcomes (11d, 42d) • Conducted in 3 countries including USA
Warwick, 2002	Study Designation: Efficacy Study Composite Score: 4 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKR • Only primary surgery • Did not use intention-to-treat analysis • Duration of followup for final and intermediate health outcomes (postoperative) • Conducted in UK
Barden, 2001	Study Designation: Efficacy Study Composite Score: 3 of 7	<ol style="list-style-type: none"> 1. Assessed final health outcomes 2. Used intention-to-treat analysis 3. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:71%; M:29%) • Only patients undergoing THR • Only primary surgery • Did not assess adverse outcomes • Conducted in Denmark
Bauer, 2001	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKR • Mainly primary surgery (revision surgery:7.5%) • Duration of followup for final and intermediate health outcomes (49d and 11d)

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Comp, 2001	Study Designation: Effectiveness Study Composite Score: 6 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 6. Adequate study duration with clinically relevant treatment 	Outcomes	<ul style="list-style-type: none"> • Duration of followup for final health outcomes (30d)
Eriksson, 2001	Study Designation: Efficacy Study Composite Score: 3 of 7	<ol style="list-style-type: none"> 1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:75%; M:25%) • Only patients undergoing HFS • Primary or revision surgery not reported • Did not use intention-to-treat analysis • Duration of followup for final and intermediate health outcomes (49d and 11d) • Conducted in 21 countries; unknown if USA also included
Fitzgerald, 2001	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted as multicenter (location unknown)
Hull, 2000	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in USA and Canada

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Kennedy, 2000	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing HFS Primary or revision surgery not reported Did not assess adverse outcomes Did not use intention-to-treat analysis Duration of followup for final and intermediate health outcomes (post-operative) Study location not reported
Colwell, 1999	Study Designation: Effectiveness Study Composite Score: 7 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Used intention-to-treat analysis 6. Adequate sample size 7. Adequate study duration with clinically relevant treatment	Population	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery
Levy, 1999	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F:79%; M:21%) Only patients undergoing TKA Primary or revision surgery not reported Did not assess adverse outcomes Small sample size (N=58) Duration of followup for final and intermediate health outcomes (post-operative) Conducted in Israel
Planes, 1999	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Adequate sample size 4. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Duration of followup for final, intermediate and adverse health outcomes (postoperative) Conducted in France

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
TIFDED Study group, 1999	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Assessed final health outcomes 2. Assessed adverse outcomes 3. Adequate sample size 4. Used intention-to-treat analysis	Population, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:79%, M:21%) • Only patients undergoing HFS • Primary versus revision surgery not reported • Duration of followup for final and intermediate health outcomes (postoperative) • Conducted in France, Belgium, Norway, Netherlands
Wakankar, 1999	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Primary or revision surgery not reported • Did not assess adverse outcomes • Small sample size (N=77) • Duration of followup for intermediate health outcomes (post-operative) • Conducted in UK
Kim, 1998	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Less stringent eligibility criteria 2. Adequate study duration with clinically relevant treatments 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Small sample size (N=100) • Mean age not reported • High male to female ratio (F:21%, M:79 %) • Only patients undergoing THR • Conducted in Korea • Only primary surgery • Duration of followup for intermediate health outcomes (post-operative) • Final health outcomes not assessed
Lassen, 1998	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed adverse outcomes 3. Adequate sample size 4. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THA • Mainly primary surgery (revision surgery 12%) • Did not assess final health outcomes • Did not use intention-to-treat analysis • Conducted in Denmark

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Rader, 1998	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Used intention-to-treat analysis 3. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only primary surgery Did not assess final health outcomes Did not assess adverse outcomes Conducted in Germany
Ryan, 1998	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled a primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis	Population, Outcomes	<ul style="list-style-type: none"> Only patients undergoing THA Only primary surgery Duration of followup for final and intermediate health outcomes (postoperative) Did not evaluate adverse outcomes Small sample size (N=100)
Warwick, 1998	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Duration of followup for final and intermediate health outcomes (post-operative) Conducted in UK
Andersen, 1997	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THA Primary or revision not reported Did not assess adverse outcomes Small sample size (N=41) Duration of followup for final health outcomes (35d) Conducted in Denmark
Dahl, 1997	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THA Mainly primary surgery (revision surgery 8%) Duration of followup for final and intermediate health outcomes (35d, 7d, 7-35d) Conducted in Norway

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Eriksson, 1997a	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Duration of followup for final and intermediate health outcomes (42d or post-operative) Conducted in Sweden & Denmark
Eriksson, 1997b	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Did not use intention-to-treat analysis Duration of followup for final and intermediate health outcomes (42d or post-operative) Conducted in 31 centers not including USA
Francis, 1997	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed adverse outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Did not assess final health outcomes Duration of followup for intermediate health outcomes (post-operative)
Nilsson, 1997	Study Designation: Effectiveness Study Composite Score: 6 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Adequate sample size 6. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THA Only primary surgery Duration of followup for final health outcomes (30d, 90d) Conducted in Sweden
Planes, 1997	Study Designation: Effectiveness Study Composite Score: 6 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 6. Adequate study duration with clinically relevant treatment	Population, Setting	<ul style="list-style-type: none"> Only patients undergoing THA Primary or revision not reported Duration of followup for final health outcomes (35d, 90d) Conducted in France

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Samama, 1997	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size.	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Conducted in France • Only primary surgery • Duration of followup for final and intermediate health outcomes (post-operative)
Eriksson, 1996	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Only primary surgery • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Europe
Kalodiki, 1996	Study Designation: Efficacy Study Composite Score: 1 of 7	1. Enrolled primary care population	Outcomes, Outcomes, Setting	<ul style="list-style-type: none"> • Small sample size (N=78) • Only patients undergoing THR • Geographic location not reported • Only primary surgery • Did not assess final health outcomes • Duration of followup for intermediate health outcomes (post-operative) • Did not assess adverse outcomes • Did not use intention to treat analysis
Laupacis, 1996	Study Designation: Effectiveness Study Composite Score: 6 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 6. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Only primary surgery • Did not assess final health outcomes • Did not assess adverse outcomes • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Canada

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Leclerc, 1996	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing TKR Mainly primary surgery (revision:7%) Duration of followup for final and intermediate health outcomes (post-operative) Conducted in Canada
Lotke, 1996	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> Primary or revision surgery not reported Did not assess final health outcomes Did not assess adverse outcomes Duration of followup for intermediate health outcomes (post-operative)
Schwartzmann, 1996	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Did not assess adverse outcomes Small sample size (N=99) Duration of followup for final and intermediate health outcomes (post-operative) Conducted in Brazil
Stannard, 1996	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Less stringent enrollment criteria 2. Assessed final health outcomes 3. Used intent to treat analysis	Population, Outcomes,	<ul style="list-style-type: none"> Only patients undergoing THR Gender not reported Low percent of revision surgery (0-12%) Duration of followup (postoperative) Did not assess adverse outcomes Small sample size (N=75)

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Stone, 1996	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Enrolled primary care population 2. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Only primary surgery • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=50) • Duration of followup for intermediate health outcomes (post-operative) • Conducted in UK
Westrich, 1996	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Less stringent eligibility criteria 2. Assessed adverse outcomes 3. Used intention-to-treat analysis	Population, Outcomes	<ul style="list-style-type: none"> • Mean age not reported • Only patients undergoing TKR • Only primary surgery (100%) • Small sample size (N=122) • Did not report final health outcomes • Duration of followup for intermediate health outcomes (post-operative)
Williams-Russo, 1996	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery • Did not assess adverse outcomes • Primary anesthetic for GA is not available in the US
Abdel-Salam, 1995	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis 4. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=80) • Conducted in England

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Avikainen, 1995	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Did not assess adverse outcomes • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Finland
Colwell, 1995	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKR • Primary or revision surgery not reported • Duration of followup for final and intermediate health outcomes (post-operative)
Warwick, 1995	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size.	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Gender not reported • Only patients undergoing THR • Conducted in United Kingdom • Duration of followup for final and intermediate health outcomes (postoperative) • Mean age not reported • Only primary surgery • Did not assess adverse outcomes
Colwell, 1994	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing THR • Mainly primary surgery (revision: 14%) • Duration of followup for final and intermediate health outcomes (post-operative or 42d)

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Fauno, 1994	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing TKR Only primary surgery Did not assess adverse outcome Duration of followup for final and intermediate health outcomes (post-operative) Conducted in Finland and Denmark
Lieberman, 1994	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate sample size 4. Used intention to treat analysis	Population, Outcomes	<ul style="list-style-type: none"> Only primary surgery Only patient undergoing THR Duration of followup for mortality and intermediate outcomes (postoperative) Did not assess adverse outcomes
Menzin, 1994	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> Only patients undergoing THR Primary or revision surgery not reported Did not assess final health outcomes Duration of followup for final and intermediate health outcomes (post-operative)
Santori, 1994	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F:74%; M:26%) Only patients undergoing THR Only primary surgery Did not assess adverse outcomes Small sample size (N=132) Duration of followup for final and intermediate health outcomes (42d) Conducted in Italy
Hull, 1993	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR and TKR Duration of followup for final and intermediate health outcomes (post-operative or 90d) Conducted in USA and Canada

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Fordyce, 1992	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Adequate study duration with clinically relevant treatments 4. Assessed adverse outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:66%; M:34%) • Only patients undergoing THR • Small sample size (N=84) • Conducted in United Kingdom • Did not assess final health outcomes • Duration of followup for intermediate health outcomes (post-operative) • Only primary surgery • Did not use intention to treat analysis
Francis, 1992	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing THR • Only primary surgery • Did not use intention-to-treat analysis • Duration of followup for final and intermediate health outcomes (post-operative)
Jorgensen, 1992	Study Designation: Efficacy Study Composite Score: 1 of 7	1. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:76%, M:24%) • Only patients undergoing HFS • Small sample size (N=82) • Conducted in Denmark • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse events • Primary or revision surgery not reported • Did not use intention to treat analysis

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Wilson, 1992	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Assessed final health outcomes 2. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:75%, M:25%) • Only patients undergoing TKR • Small sample size (N=59) • Conducted in the United Kingdom • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse events • Primary or revision surgery not reported
Bailey, 1991	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Used intention-to-treat analysis	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing THR • Small sample size (N=95) • Duration of followup for final and intermediate health outcomes (post-operative)
Eriksson, 1991	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Did not use intention-to-treat analysis • Small sample size (N=136) • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Sweden
Jorgensen, 1991	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing TKA • Primary or revision surgery not reported • Did not assess adverse outcomes • Small sample size (N=48) • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Denmark

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Lassen, 1991	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Adequate sample size.	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Conducted in Denmark Duration of followup for final and intermediate health outcomes (postoperative) Only primary surgery Did not use intention to treat analysis Did not assess adverse outcomes
Levine, 1991	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Primary or revision surgery not reported Duration of followup for final and intermediate health outcomes (post-operative) Conducted in Canada
Mitchell, 1991	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> Only patients undergoing TKA Only primary surgery Did not assess final health outcomes Did not assess adverse outcomes Small sample size (N=72) Duration of followup for final and intermediate health outcomes (post-operative) Drug regimen used for epidermal anesthesia was NR, agents used for GA are not available/limited availability in the US
Planes, 1991	Study Designation: Efficacy Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only patients undergoing THR Only primary surgery Duration of followup for final and intermediate health outcomes (post-operative) Primary anesthetics used are not available in the US Conducted in France

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Torholm, 1991	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Enrolled primary care population 2. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Small sample size (N=120) • Conducted in Denmark • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse events • Did not use intention to treat analysis
Woolson, 1991	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Adequate sample size 5. Intention to treat analysis	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing THR • Duration of followup for intermediate and final health outcomes (postoperative) • Did not assess adverse outcomes
Haas, 1990	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKR • Only primary surgery • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=119) • Duration of followup for intermediate health outcomes (post-operative)
Sorensen, 1990	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Small sample size (N=70) • Conducted in Denmark • Mean age not reported • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse outcomes events • Primary or revision surgery not reported • Did not use intention to treat analysis

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Dechavanne, 1989	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Did not assess final health outcomes • Did not assess adverse outcomes • Small sample size (N=124) • Duration of followup for intermediate health outcomes (post-operative) • Conducted in France
Monreal, 1989	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:82%; M:18%) • Only patients undergoing HFS • Primary or revision surgery not reported • Did not assess adverse outcomes • Did not use intention-to-treat analysis • Small sample size (N=90) • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in Spain
Powers, 1989	Study Designation: Effectiveness Study Composite Score: 6 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size 6. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:72%, M:28%) • Only patients undergoing HFS • Conducted in Canada • Primary or revision surgery not reported • Duration of followup for final health outcomes (21-90d)
Planes, 1988	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Duration of followup for final and intermediate health outcomes (post-operative) • Conducted in France

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Barre, 1987	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care 2. Assessed final health outcomes 3. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Did not assess adverse outcomes • Small sample size (N=80) • Duration of followup for final and intermediate health outcomes (60d) • Conducted in France
Palement, 1987	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> • Age and gender not reported • Only patients undergoing THR • Primary or revision surgery not reported • Duration of followup for final and intermediate health outcomes (post-operative)
McKenzie, 1985	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:75%; M:25%) • Only patients undergoing HFS • Primary or revision surgery not reported • Did not assess adverse outcomes • Small sample size (N=48) • Duration of followup for final and intermediate health outcomes (post-operative) • Primary anesthetics used are not available in the US • Conducted in UK
Alfaro, 1986	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Small sample size (N=90) • Conducted in Spain • Duration of followup for final and intermediate health outcomes (post-operative) • Did not assess adverse events • Primary or revision surgery not reported

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Turpie, 1986	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Small sample size (N=100) • Conducted in Canada • Duration of followup for final and intermediate health outcomes (postoperatively) • Primary or revision surgery not reported
Welin-Berger, 1982	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Assessed final health outcomes 2. Used intention-to-treat analysis	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:72%, M:28%) • Only patients undergoing THR • Small sample size (N=40) • Conducted in Sweden • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse events • Primary or revision surgery not reported
Modig, 1981	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Used intention-to-treat analysis 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only patients undergoing THR • Primary or revision surgery not reported • Did not assess adverse outcomes • Small sample size (N=30) • Duration of followup for final and intermediate health outcomes (14d) • Primary anesthetic used for GA is not available in the US • Conducted in Sweden

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
McKenna, 1980	Study Designation: Efficacy Study Composite Score: 1 of 7	1. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • High female to male ratio (F:90%, M:10%) • Only patients undergoing TKR • Small sample size (N=21) • Duration of followup for final and intermediate health outcomes (postoperative) • Did not assess adverse events • Primary or revision surgery not reported • Did not use intention to treat analysis

Abbreviations: d=days; F=female; HFS=hip fracture surgery; M=male; N=total population; THA=total hip arthroplasty; TKA=total knee arthroplasty; TKR=total knee replacement; THR=total hip replacement;

Table 99. Evaluation of applicability for individual randomized controlled trials in nonmajor orthopedic surgery

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Lapidus, 2007	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Duration of followup for final health outcomes (45d) • Conducted in Sweden

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Michot, 2002	Study Designation: Efficacy Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Used intention-to-treat analysis 5. Adequate study duration with clinically relevant treatment 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Duration of followup for final health outcomes (30d) • Conducted in Switzerland

Abbreviations: d=days; F=female; M=male; N=total population

Table 100. Evaluation of applicability for individual observational studies

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Bozic, 2010	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Adequate sample size 	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKR • Only primary surgery (100%) • Did not use intention-to-treat analysis • Duration of followup for final health outcome (30d)
Gerken, 2010	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Primary versus revision surgery not reported • Duration of followup for all outcomes (during hospital stay) • Did not use intention-to-treat analysis • Conducted in Belgium

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Cusick, 2009	Study Designation: Effectiveness Study Composite Score: 5 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Adequate sample size 5. Adequate study duration with clinically relevant treatment	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only primary surgery (100%) Gender not reported Did not assess adverse outcomes Did not use intention-to-treat analysis Duration of followup for mortality (90d) Conducted in Ireland
Froimson, 2009	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Adequate sample size	Population, Outcomes	<ul style="list-style-type: none"> Only primary surgery (100%) Gender not reported Did not assess adverse outcomes Did not use intention-to-treat analysis Duration of followup for final health outcomes (30d)
Gandhi, 2009	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Adequate study duration 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> Only primary surgery Did not assess final health outcomes Did not assess adverse outcomes Conducted in Canada Did not use intention- to-treat analysis
McNamara, 2009	Study Designation: Efficacy Study Composite Score: 4 of 7	1. Less stringent eligibility criteria 2. Adequate study duration 3. Assessed final health outcomes 4. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> High female to male ratio (F=78.5%: M=21.5%) Did no report primary or secondary surgery Did not assess adverse outcomes Conducted in UK Did not use intention-to- treat analysis

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Dorr, 2007	Study Designation: Effectiveness Study Composite Score: 5 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Adequate study duration 4. Assessed final health outcomes 5. Adequate sample size 	Population, Outcomes	<ul style="list-style-type: none"> • Only primary surgery • Did not assess adverse outcomes • Did not use intention-to-treat analysis
Shorr, 2007	Study Designation: Efficacy Study Composite Score: 4 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Assessed final health outcomes 3. Assessed adverse outcomes 4. Adequate sample size 	Population, Outcomes	<ul style="list-style-type: none"> • Primary or secondary surgery not reported • Duration of followup for final health outcomes (in-hospital) • Did not use intention-to-treat analysis
Leirozovicz, 2004	Study Designation: Efficacy Study Composite Score: 3 of 7	<ol style="list-style-type: none"> 1. Less stringent eligibility criteria 2. Assessed final health outcomes 3. Adequate sample size 	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Only primary surgery • Did not assess adverse outcomes • Duration of followup for final health outcomes (30d) • Conducted in Asia • Did not use intention-to-treat analysis
Sachs, 2003	Study Designation: Effectiveness Study Composite Score: 6 of 7	<ol style="list-style-type: none"> 1. Enrolled primary care population 2. Less stringent eligibility criteria 3. Assessed final health outcomes 4. Assessed adverse outcomes 5. Adequate sample size 6. Adequate study duration with clinically relevant treatments 	Population, Outcomes	<ul style="list-style-type: none"> • Only patients undergoing TKA • Only primary surgery (100%) • Duration of followup for mortality (90d) • Did not use intention-to-treat analysis

Author, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Ryan, 1998	Study Designation: Efficacy Study Composite Score: 3 of 7	1. Enrolled primary care population 2. Assessed adverse outcomes 3. Adequate sample size	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Did not report primary or secondary surgery • Did not assess final health outcomes • Duration of followup for intermediate and adverse health outcomes (postoperative) • Conducted in USA and Canada • Did not use intention-to-treat analysis
Lemos, 1991	Study Designation: Efficacy Study Composite Score: 2 of 7	1. Less stringent eligibility criteria 2. Assessed final health outcomes	Population, Outcomes, Setting	<ul style="list-style-type: none"> • Did not report male or female percentage • Did not report primary or secondary surgery • Did not assess adverse outcomes • Duration of followup for final health outcomes (postoperative) • Small sample size (240) • Did not use intention-to-treat analysis

Abbreviations: TKR=total knee replacement; THR=total hip replacement; TKA=total knee replacement

Table 101. Strength of applicability for the body of evidence evaluating the link between deep vein thrombosis and pulmonary embolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Relationship between deep vein thrombosis and pulmonary embolism in major orthopedic surgery	Moderate	There is insufficient evidence to determine the relationship between intermediate and final health outcomes in patients who had major orthopedic surgery. Overall applicability is limited because the majority of data is within knee replacement surgery (57.8%) and little is within hip fracture surgery (4.4%). However, the majority of data is derived from trials conducted in the United States and published in the 1990's.

Table 102. Strength of applicability for the body of evidence evaluating symptomatic venous thromboembolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of symptomatic venous thromboembolism in total hip replacement	NA	No data
Incidence of symptomatic venous thromboembolism in total knee replacement	NA	No data
Incidence of symptomatic venous thromboembolism in hip fracture surgery	NA	No data
Impact of congestive heart failure	Moderate	Congestive heart failure significantly increases the odds of symptomatic objectively confirmed venous thromboembolism. Data is highly applicable to primary major orthopedic surgery although only one of the two studies was conducted in the United States which did not include hip fracture surgery.
Impact of inactive cancer	Moderate	Inactive cancer significantly increases the odds of symptomatic objectively confirmed venous thromboembolism. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of hormone replacement therapy	Moderate	Hormone replacement therapy significantly increases the odds of symptomatic objectively confirmed venous thromboembolism. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of age	Moderate	Age did not influence the odds of symptomatic objectively confirmed venous thromboembolism. Data is applicable to all three major orthopedic surgeries although the trial evaluating hip fracture surgery was conducted in the United Kingdom.
Impact of living at home	Low	Living at home significantly increases the odds of symptomatic objectively confirmed venous thromboembolism. Data is more applicable to females than males and is highly applicable to hip fracture surgery although the trial was conducted in the United Kingdom. Data is not applicable to knee or hip replacement surgery.
Impact of intertrochanteric fracture	Low	Intertrochanteric fractures significantly increases the odds of symptomatic objectively confirmed venous thromboembolism. Data is more applicable to females than males and is highly applicable to hip fracture surgery although the trial was conducted in the United Kingdom. Data is not applicable to knee or hip replacement surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Impact of subtrochanteric fracture	Low	Subtrochanteric fractures significantly increases the odds of symptomatic objectively confirmed venous thrombembolism. Data is more applicable to females than males and is highly applicable to hip fracture surgery although the trial was conducted in the United Kingdom. Data is not applicable to knee or hip replacement surgery.
Impact of elevated hemoglobin	Low	Elevated hemoglobin significantly increases the odds of symptomatic objectively confirmed venous thrombembolism. Data is more applicable to females than males and is highly applicable to hip fracture surgery although the trial was conducted in the United Kingdom. Data is not applicable to knee or hip replacement surgery.
Impact of gender	Low	Male gender did not influence the odds of symptomatic objectively confirmed venous thrombembolism. Data is more applicable to females than males and is highly applicable to hip fracture surgery although the trial was conducted in the United Kingdom. Data is not applicable to knee or hip replacement surgery.
Impact of history of venous thrombembolism	Low	History of venous thrombembolism significantly increases the odds of symptomatic objectively confirmed venous thrombembolism. Data is applicable to all major orthopedic surgeries although the trial was conducted in Asia and therefore overall applicability is limited.
Impact of varicose veins	Low	Varicose veins significantly increases the odds of symptomatic objectively confirmed venous thrombembolism. Data is applicable to all major orthopedic surgeries although the trial was conducted in Asia and therefore overall applicability is limited.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared with no prophylaxis, patients who received pharmacological prophylaxis did not have a difference in the odds of symptomatic objectively confirmed venous thromboembolism. Data is highly applicable to patients who had total hip replacement surgery and received fondaparinux prophylaxis. Applicability is limited because of a high female percentage, the trial was conducted in Japan, and the followup was 11 days.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared with injectable unfractionated, patients who had major orthopedic surgery and received injectable low molecular weight heparin did not have a difference in the odds of symptomatic venous thromboembolism. Data is highly applicable to injectable low molecular weight heparin agents versus injectable unfractionated heparin in patients undergoing total hip replacement during the first 42 days after surgery. Applicability is limited because the type of surgery; primary or revision was not reported and because the one available trial was conducted in Turkey.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Moderate	Compared with injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received low molecular weight heparin agents did not have a difference in the odds of symptomatic venous thromboembolism. Data is highly applicable to primary or revision total hip replacement surgery. Data has a low level of applicability to primary or revision surgery for total knee replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared with received oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of symptomatic venous thromboembolism. Data is highly applicable to total knee or hip replacement surgery and is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression versus intermittent pneumatic compression devices	NA	No data
Intermittent pneumatic compression by Kendall versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decreased risk of symptomatic venous thromboembolism. Applicability is limited because the majority of trials were conducted outside of the United States. Data is highly applicable to primary hip replacement surgery with the use of injectable low molecular weight heparin agents. Data has a low level of applicability to the use of injectable factor Xa inhibitors, oral vitamin K antagonists, revision surgery, and total knee replacement surgery. Data is moderately applicable to hip fracture surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 103. Strength of applicability for the body of evidence evaluating major venous thromboembolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of major venous thromboembolism in total hip replacement	NA	No data
Incidence of major venous thromboembolism in total knee replacement	NA	No data
Incidence of major venous thromboembolism in hip fracture surgery	NA	No data
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared with no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had a decreased risk of major venous thromboembolism. Data is highly applicable to dabigatran, primary total knee replacement surgery but is not applicable to total hip replacement or hip fracture surgery. Applicability is limited due to the short duration of followup and because the only trial available was conducted in Japan.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared with injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of major venous thromboembolism. Data is moderately applicable to primary total hip replacement surgery. Data has low applicability to primary total knee replacement surgery. Data is not applicable to primary or revision surgery for hip fracture. Applicability is limited because all trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression by Kendall versus the Venaflo intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days of prophylaxis did not have a difference in the odds of major venous thromboembolism. Applicability is limited because the trial was conducted in Italy. Data is highly applicable to the use of oral vitamin K antagonists and to primary total hip replacement. Data is not applicable to primary or revision total knee replacement or hip fracture surgery or other pharmacologic methods of prophylaxis.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 104. Strength of applicability for the body of evidence evaluating pulmonary embolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of pulmonary embolism in total hip replacement	Low	The pooled incidence of pulmonary embolism in patients who had total hip replacement surgery was 6 percent. Overall applicability is limited because all trials were conducted outside of the United States and four of the five trials were published in the 1980's.
Incidence of pulmonary embolism in total knee replacement	Low	The pooled incidence of pulmonary embolism in patients who had total knee replacement surgery was 1 percent. Overall applicability is limited because both trials were conducted outside of the United States.
Incidence of pulmonary embolism in hip fracture surgery	Low	Based on one trial, the incidence of pulmonary embolism was 3 percent in patients who had hip fracture surgery. Overall applicability is limited because this trial was conducted in Canada and published in 1989.
General versus regional anesthesia	Low	There is insufficient data to determine the impact of general versus regional anesthesia on the risk of pulmonary embolism. Data is not applicable to knee replacement or hip fracture surgery. Data is highly applicable to hip replacement surgery although both trials were conducted outside of the United States with anesthetics currently unavailable in the United States.
Cemented versus noncemented arthroplasty	Low	There was insufficient data to determine the impact of cemented versus noncemented arthroplasty on the risk of pulmonary embolism. Data is highly applicable to primary hip replacement surgery although overall applicability is limited as this trial was conducted in Canada and had a short duration of followup. Data is not applicable to knee replacement or hip fracture surgery.
Impact of age	Moderate	Age increases the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of genitourinary infection	Moderate	Genitourinary infection increases the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of cardiovascular disease	Moderate	Cardiovascular disease decreases the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of phlebitis	Moderate	Phlebitis has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of thyroid hormone replacement therapy	Moderate	Thyroid hormone replacement therapy has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of a history of pulmonary embolism	Moderate	History of pulmonary embolism has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of varicosity	Moderate	Varicosity has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.

Comparison	Strength of applicability	Conclusion with description of applicability
Impact of phlebitis in the other extremity	Moderate	Phlebitis in the other extremity has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Impact of peripheral vascular disease	Moderate	Peripheral vascular disease has no impact on the odds of pulmonary embolism. Data is applicable to hip or knee replacement surgery although is not applicable to hip fracture surgery. Overall applicability is limited due to shorter duration of followup.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the odds of pulmonary embolism. Data is highly applicable to total hip replacement. Applicability to total knee replacement and primary versus revisions surgery is limited. Data is not applicable to hip fracture surgery. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared with oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of pulmonary embolism. Data is highly applicable to hip fracture surgery. Applicability is limited because the type of surgery; primary or revision was not reported. Data is not applicable to primary or revision total hip or knee replacement surgery.
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared with mechanical prophylaxis, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of pulmonary embolism. Data is highly applicable to primary hip fracture surgery. Data is not applicable to primary or revision total hip or knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared with injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin had a decreased in the odd of pulmonary embolism. Data is moderately applicable to total hip replacement surgery. Data has limited applicability to total knee and hip fracture surgery. Applicability is limited because the type of surgery; primary or revision was not reported, there was a short duration of follow up and the majority of trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared with injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of pulmonary embolism. Data is highly applicable to revision surgery for total knee replacement and total hip replacement surgery. Although the one trial evaluating hip replacement was conducted in Japan. Data is not applicable to hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared with injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and injectable low molecular weight heparin agents did not have a difference in the risk of pulmonary embolism. Data is moderately applicable to primary total hip replacement surgery. Data has low applicability to primary total knee replacement surgery. Applicability is limited because all of the trials were conducted outside of the United States. Data is not applicable to primary or revision surgery for hip fracture.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared with oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of pulmonary embolism. Applicability is limited due to the short duration of follow up. Data has high applicability to total hip replacement surgery and moderate applicability to total knee replacement surgery. Data is not applicable to hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared with mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of pulmonary embolism. Data is highly applicable primary total hip replacement surgery. Data is not applicable to primary or revision total knee or hip fracture surgery and has limited applicability because the one available trial was conducted in the United Kingdom.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared with injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable unfractionated heparin did not have a difference in the odds of pulmonary embolism. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee or hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression by Kendall versus Venaflow intermittent pneumatic compression devices	Low	Compared to intermittent pneumatic compression device by Kendall, patients who had major orthopedic surgery and received prophylaxis with the Venaflow intermittent pneumatic compression device did not have a difference in the odds of pulmonary embolism. Data is highly applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Moderate	Compared with pharmacologic prophylaxis alone, patient who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis had no difference in the odds of pulmonary embolism. Data is highly applicable to total hip replacement surgery, moderately applicable to total knee replacement surgery and not applicable to hip fracture surgery or revision surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	Low	Compared with mechanical prophylaxis alone, patient who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis had no difference in the risk of pulmonary embolism. Applicability is limited due to the short duration of followup. Data is highly applicable to primary or revision total hip replacement surgery and not applicable to total knee replacement or hip fracture surgery.
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decrease in the odds of pulmonary embolism. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is moderately applicable to the used of injectable low molecular weight heparin agents and has a low level of applicability to the use of injectable factor Xa inhibitors and oral vitamin K antagonists. Data is highly applicable to primary or revision total hip replacement surgery. Data has a low level of applicability to hip fracture surgery and is not applicable to knee replacement surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=not applicable

Table 105. Strength of applicability for the body of evidence evaluating fatal pulmonary embolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of fatal pulmonary embolism in total hip replacement	Low	Based on one trial, the incidence of fatal pulmonary embolism was zero percent in patients who had total hip replacement surgery. Overall applicability is limited because this trial was conducted in Canada and published in 1986.
Incidence of fatal pulmonary embolism in total knee replacement	Low	Based on one trial the incidence of fatal pulmonary embolism was 0 percent. Overall applicability is limited because this trial was conducted in the United Kingdom.
Incidence of fatal pulmonary embolism in hip fracture surgery	Low	Based on one trial, the incidence of fatal pulmonary embolism was 0 percent in patients who had hip fracture surgery. Overall applicability is limited because this trial was conducted in Canada and published in 1989.
Tissue fibrin adhesive versus none	Low	Compared to surgery without tissue fibrin adhesive, patients who received tissue fibrin adhesive did not have a difference in the risk of fatal pulmonary embolism. Data is highly applicable to knee replacement surgery although is limited because the trial was conducted in Israel and had shorter duration of followup. Data is not applicable to other major orthopedic surgeries.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the odds of fatal pulmonary embolism. Data is applicable to total hip replacement but has limited applicability to total knee replacement and hip fracture surgery. Data has limited applicability to primary and revision surgery. Applicability is limited due to the short duration of follow up.
Mechanical prophylaxis versus no prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared with oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of fatal pulmonary embolism. Data is highly applicable to hip fracture surgery. Applicability is limited because the type of surgery; primary or revision was not reported. Data is not applicable to primary or revision total hip or knee replacement surgery.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin did not have a difference in the odds of fatal pulmonary embolism. Data is highly applicable to total knee replacement surgery. Applicability is limited because the type of surgery; primary or revision was not reported and due to the short duration of follow up. Data is not applicable to total hip replacement or hip fracture surgery,
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of fatal pulmonary embolism. Data is moderately applicable to primary or revision for total hip replacement surgery. Applicability is limited for primary or revision surgery in the total knee and hip fracture surgery population and because the majority of trials were conducted outside of the United States
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin, patients who had major orthopedic surgery and received inhibitors injectable low molecular weight heparin agents did not have a difference in the odds of fatal pulmonary embolism. Data is moderately applicable to primary or revision total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery and overall has limited applicability because the trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of fatal pulmonary embolism. Data is highly applicable to primary total hip replacement and is not applicable to other major orthopedic surgeries. Applicability is limited due to the short duration of follow up.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of fatal pulmonary embolism. Data is highly applicable to primary total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of fatal pulmonary embolism. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Intermittent pneumatic compression by Kendall versus the Venaflo intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the odds of fatal pulmonary embolism. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of injectable factor Xa inhibitors during hip fracture surgery. Data is not applicable to primary or revision total hip or total knee replacement surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=not applicable

Table 106. Strength of applicability for the body of evidence evaluating nonfatal pulmonary embolism in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of nonfatal pulmonary embolism in total hip replacement	Low	Based on one trial, the incidence of nonfatal pulmonary embolism was 2 percent in patients who had total hip replacement surgery. Overall applicability is limited because this trial was conducted in Canada and published in 1986.

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of nonfatal pulmonary embolism in total knee replacement surgery	Low	Based on one trial the incidence of nonfatal pulmonary embolism was 0 percent. Overall applicability is limited because this trial was conducted in the United Kingdom.
Incidence of fatal pulmonary embolism in hip fracture surgery	Low	Based on one trial, the incidence of nonfatal pulmonary embolism was 3 percent in patients who had hip fracture surgery. Overall applicability is limited because this trial was conducted in Canada and published in 1989.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the odds of nonfatal pulmonary embolism. Data is applicable to total hip replacement but has limited applicability to total knee replacement and hip fracture surgery. Data has limited applicability to primary and revision surgery. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the percent of nonfatal pulmonary embolism. Data is moderately applicable to primary total hip and total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared with injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of nonfatal pulmonary embolism. Applicability is limited due to the short duration of follow up. Data is moderately applicable to total hip replacement surgery. Applicability is limited because the type of surgery; primary or revision is not reported and because the majority of the trials were conducted outside of the United States. Applicability to total knee replacement and hip fracture surgery is limited.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of nonfatal pulmonary embolism. Data is moderately applicable to primary or revision for total hip replacement surgery. Applicability is limited for primary or revision surgery in the total knee and hip fracture surgery population.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of nonfatal pulmonary embolism. Data is moderately applicable to primary or revision total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of nonfatal pulmonary embolism. Data is highly applicable to primary or revision total knee replacement surgery and is not applicable to other major orthopedic surgeries. Applicability was limited due to the short duration of follow up.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received, injectable low molecular weight heparin agents did not have a difference in the odds of nonfatal pulmonary embolism. The data is highly applicable to primary total hip replacement surgery. The data is not applicable to primary or revision total knee or hip fracture surgery and has limited applicability because the trial was conducted in United Kingdom.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable unfractionated heparin did not have a difference in the odds of nonfatal pulmonary embolism. Applicability is limited by the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee or hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of nonfatal pulmonary embolism. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Intermittent pneumatic compression by Kendall versus the Venaflow intermittent pneumatic compression device	Low	Compared to the intermittent pneumatic compression device by Kendall, patients who had major orthopedic surgery and received the Venaflow intermittent pneumatic compression device did not have a difference in the odds of nonfatal pulmonary embolism. Applicability is limited due to the short duration of follow up. Data is moderately applicable to primary or revision total hip replacement surgery. Data is moderately applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	Moderate	Compared to the Flowtron device, patients who had major orthopedic surgery and received ActiveCare device did not have a difference in the odds of nonfatal pulmonary embolism. Data is highly applicable to total hip or knee replacement surgery but is not applicable to hip fracture surgery.
Intermittent pneumatic compression versus graduated compression	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Moderate	Compared with pharmacologic prophylaxis alone, patient who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis had no difference in the odds of nonfatal pulmonary embolism. Data is highly applicable to total hip replacement surgery, moderately applicable to total knee replacement surgery and not applicable to hip fracture surgery or revision surgery.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had decreased odds of nonfatal pulmonary embolism. Applicability is limited because the included trials were conducted outside of the United States. Data is moderately applicable to the use of injectable low molecular weight heparin agents during primary total hip replacement surgery. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors or to hip fracture surgery. Data is not applicable to knee replacement surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=not applicable

Table 107. Strength of applicability for the body of evidence evaluating post thrombotic syndrome in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression by Kendall versus the Venaflo	NA	No data
Intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 108. Strength of applicability for the body of evidence evaluating mortality in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the odds of mortality. Data is highly applicable to hip replacement surgery, but has limited applicability to total knee replacement and hip fracture surgery. Data has limited applicability to primary and no applicability to revision surgery. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the risk of mortality. Applicability is limited because the type of surgery; primary or revision was not reported. Data is highly applicable to the hip fracture surgery. Data is not applicable to primary or revision total hip or knee replacement surgery.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality. Applicability is limited by the short duration of follow up and because the majority of trials were conducted outside of the United States. Applicability is limited because the type of surgery; primary or revision is not reported. Data is moderately applicable to total hip replacement and hip fracture surgery. Data is not applicable to total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality. Applicability is limited by the duration of follow up. Data has moderate applicability to primary or revision total hip replacement surgery. Data has a low level of applicability to primary hip fracture surgery and revision total knee replacement surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of mortality. Applicability is limited by the duration of follow up and because the majority of trials were conducted outside of the United States. Data is moderately applicable to primary total knee or total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary or revision total knee and hip replacement surgery but not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is moderately applicable to primary total knee and hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin patients who had major orthopedic surgery and inhibitors injectable unfractionated heparin did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up. Applicability is limited because the type of surgery; primary or revision is not reported and because the trials were conducted outside of the United States. Data is moderately applicable to total knee and hip replacement and hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	Low	Compared to injectable unfractionated heparin patients who had major orthopedic surgery and received injectable or oral factor Xa inhibitors had a decreased rate of mortality. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee or hip fracture surgery.
Injectable unfractionated heparin versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable unfractionated heparin did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up and because the trial was conducted in Italy. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to revision or primary total knee replacement or hip fracture surgery.
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to revision or primary total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression by Kendall versus the Venaflow intermittent pneumatic compression device	Low	Compared to the intermittent pneumatic compression device by Kendall, patients who had major orthopedic surgery and received intermittent pneumatic compression device by Venaflow did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Low	Compared with pharmacologic prophylaxis alone, patient who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis do not have a difference in the odds of mortality. Data is highly applicable to patients who had primary total hip replacement surgery and received aspirin plus IPC versus aspirin alone. Data is not applicable to other major orthopedic or revision surgeries.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the odds of mortality. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is moderately applicable to the use of injectable low molecular weight heparin agents. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data is highly applicable to primary total hip replacement surgery, moderately applicable to hip fracture surgery and has low applicability to hip fracture surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 109. Strength of applicability for the body of evidence evaluating mortality due to bleeding in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the odds of mortality due to bleeding. Data is highly applicable to the use of enoxaparin or fondaparinux in hip replacement surgery, but has limited applicability to total knee replacement and hip fracture surgery. Data has limited applicability to primary and no applicability to revision surgery. Applicability is limited due to the short duration of follow up and because the trials available was conducted in Denmark and Japan.
Mechanical prophylaxis versus no prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to unfractionated heparin, patients who had major orthopedic surgery and injectable low molecular weight heparin agents did not have a difference in the odds of mortality due to bleeding. Applicability is limited due to the short duration of follow up and because the available trial was conducted in Spain. Data is highly applicable to primary hip fracture surgery. Data is not applicable to primary or revision total knee or hip replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents, did not had a difference in the odds of mortality due to bleeding. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary hip fracture surgery. Data is not applicable to primary or revision total knee or hip replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not had a difference in the risk of mortality due to bleeding. Applicability is limited due to the short duration of follow up and because the trial was conducted outside of the United States. Data is highly applicable to primary total knee replacement surgery. Data is not applicable to primary or revision hip fracture or total hip replacement surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality due to bleeding. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary total knee replacement surgery. Data is not applicable to primary or revision hip fracture or total hip replacement surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of mortality due to bleeding. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision hip fracture or total knee replacement surgery.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression by Kendall versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 110. Strength of applicability for the body of evidence evaluating health related quality of life in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression by Kendall versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 111. Strength of applicability for the body of evidence evaluating deep vein thrombosis in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of deep vein thrombosis in patients who had total hip replacement surgery	Low	The pooled incidence of deep vein thrombosis in patients who had total hip replacement surgery was 39 percent. Overall applicability is limited because seven of the eight trials were conducted outside of the United States while the eight did not report location.
Incidence of deep vein thrombosis in patients who had total knee replacement surgery	Low	The pooled incidence of deep vein thrombosis in patients who had total knee replacement surgery was 46 percent. Overall applicability is limited because the majority of data is derived from the study conducted in Singapore while only a small percent (<10 percent) of data is derived from the study conducted in the United States. One trial was published in 2009 while the other in 1980.
Incidence of deep vein thrombosis in patients who had hip fracture surgery	Low	Based on one trial, the incidence of deep vein thrombosis was 47 percent in patients who had hip fracture surgery. Overall applicability is limited because the trial was conducted in Denmark and published in 1992.
General versus regional anesthesia	Low	Patients who received general anesthesia may have a higher risk of deep vein thrombosis compared to those who received regional anesthesia in major orthopedic surgery. Overall applicability is limited as the majority of trials were conducted outside of the United States using anesthetics that are not available in the United States, additionally followup was generally shorter and primary versus revision surgery was usually not reported.
Cemented versus cementless arthroplasty	Low	Compared to patients who had cementless arthroplasty, those who had cemented arthroplasty had no difference in the risk of deep vein thrombosis. Data is highly applicable to hip replacement surgery although overall applicability is limited as the majority of studies were conducted outside of the United States and had a short duration of followup. Data is not applicable to knee replacement or hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Bone vacuum cement versus standard procedure	Low	Compared to standard procedure, patients who received bone vacuum cement had a lower risk of deep vein thrombosis. Data is highly applicable to primary total knee replacement surgery although overall applicability is limited as the trial was conducted in Germany and had a short duration of followup. Data is not applicable to hip replacement or hip fracture surgery.
Limited time in flexion/dislocation versus standard procedure	Low	Compared to standard procedure, patients whose limb was in flexion and dislocation for a limited time did not have a difference in the risk of deep vein thrombosis. Data is highly applicable to primary hip replacement surgery although the duration of followup was short. Data is not applicable to other major orthopedic surgeries.
Primary versus revision surgery	Low	Compared to revision surgery, primary surgery impacts the risk of deep vein thrombosis (although direction or magnitude is unknown). Data is highly applicable to hip replacement surgery and not applicable to other major orthopedic surgeries.
Impact of perioperative blood loss	Low	Perioperative blood loss does not impact the odds of deep vein thrombosis. Data is highly applicable to hip replacement surgery and not applicable to other major orthopedic surgeries.
Impact of blood transfusions	Low	Blood transfusion does not impact the odds of deep vein thrombosis. Data is highly applicable to hip replacement surgery and not applicable to other major orthopedic surgeries.
Impact of operative time	Low	Operative time does not impact the odds of deep vein thrombosis.
Impact of age	Low	Age increases the odds of deep vein thrombosis. Data is highly applicable to hip replacement surgery although most data is derived from trials conducted outside of the United States. Data is not applicable to knee replacement or hip fracture surgery.
Impact of obesity / weight	Low	There is insufficient data to determine the impact of obesity / weight on deep vein thrombosis. Data is highly applicable to hip replacement surgery although both studies were conducted outside of the United States. Data is not applicable to knee replacement or hip fracture surgery.
Impact of gender	Low	There is insufficient data to determine the impact of gender on deep vein thrombosis. Data is highly applicable to hip replacement surgery and is not applicable to knee replacement or hip fracture surgery.
Impact of smoking	Low	There is little to no effect of smoking on the odds of deep vein thrombosis (although magnitude and direction are unknown). Data is highly applicable to hip replacement surgery although the trial was conducted outside of the United States. Data is not applicable to knee replacement or hip fracture surgery.
Impact of height	Low	Height does not impact the odds of deep vein thrombosis. Data is highly applicable to hip replacement surgery and is not applicable to knee replacement or hip fracture surgery.
Impact of Factor V Leiden mutation	Moderate	Factor V Leiden mutation does not impact the odds of deep vein thrombosis. Data is applicable to hip or knee replacement surgery although not applicable to hip fracture surgery. Overall applicability is limited due to a shorter duration of followup.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had a decrease in the risk of deep vein thrombosis. Data is highly applicable to primary hip replacement surgery, but has limited applicability to total knee replacement and hip fracture surgery. The data has no applicability to revision surgery. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Mechanical prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received mechanical prophylaxis had a decrease in the risk of deep vein thrombosis. Data is highly applicable to patients receiving prophylaxis with venous foot pump undergoing primary total hip replacement but not applicable to total hip replacement or hip fracture surgery. Applicability is limited due to the short duration of follow up and because the one available trial was conducted in the United Kingdom.
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is moderately applicable to primary or revision total hip and total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis patients who had major orthopedic surgery and received oral antiplatelet agents had an increased risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is moderately applicable to primary total knee replacement and hip fracture surgery. Data is not applicable to primary or revision total hip replacement surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decreased risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States. Applicability to primary or revision surgery is limited. Data is moderately applicable to total hip replacement surgery. Data has a low level of applicability to total knee and hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increased risk of deep vein thrombosis. Data is highly applicable to hip replacement and hip fracture surgery. Data is not applicable to knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increased risk of deep vein thrombosis. Data is highly applicable to primary total hip replacement. Data is not applicable to primary or revision total knee or hip fracture surgery and has limited applicability because the trial was conducted outside of the United States.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared to oral vitamin K antagonists, patients who received injectable low molecular weight heparin agents had a decreased risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data has high applicability to primary or revision total hip or knee replacement surgery And is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who received injectable low molecular weight heparin agents did not have a difference in the risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up and because all trials were conducted outside of the United States. Data is moderately applicable to primary total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable unfractionated heparin had an increased risk of deep vein thrombosis. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery and has limited applicability because all trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable unfractionated heparin had an increased risk of deep vein thrombosis. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery and has limited applicability because the trial was conducted in Italy.
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists did not have a difference in the risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up. Applicability is limited base on the type of surgery; primary or revision. Data is highly applicable to total hip replacement surgery. Data is not applicable to total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the trials wer conducted outside of the United States. Data has a low level of applicability to primary total hip replacement and hip fracture surgery. Data is not applicable to primary or revision total knee replacement surgery.
Intermittent pneumatic compression device by Kendall versus Venaflow intermittent pneumatic compression device	Low	Compared to the intermittent pneumatic compression device by Kendall, patients who had major orthopedic surgery and received intermittent pneumatic compression device by Venaflow had a decreased risk of deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is moderately applicable to primary or revision total hip replacement surgery. Data is moderately applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	Moderate	Compared to the Flowtron device, patients who had major orthopedic surgery and received ActiveCare device did not have a difference in the percent of deep vein thrombosis. Data is highly applicable to total hip or knee replacement surgery but is not applicable to hip fracture surgery.
Intermittent pneumatic compression versus graduated compression	Low	Compared to graduated compression stockings, patient who had major orthopedic surgery and received intermittent pneumatic compression devices had a decreased risk of deep vein thrombosis. Data is highly applicable to the Venaflow intermittent pneumatic compression device and Comprinet Pro graduated compression stockings. Data is highly applicable to total hip or knee replacement surgery but is not applicable to hip fracture surgery. Overall applicability is limited because the trial was conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Moderate	Compared with pharmacologic prophylaxis alone, patients who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis had a decreased risk of deep vein thrombosis. Data is highly applicable to primary total hip or total knee replacement surgery, has limited applicability to revision surgery and is not applicable to hip fracture surgery.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decreased risk of deep vein thrombosis. Data is highly applicable to the use of injectable low molecular weight heparin agents although applicability is limited because the majority of trials were conducted outside of the United States. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data is highly applicable to primary or revision total hip replacement surgery, moderately applicable to hip fracture surgery and has low applicability to total knee replacement surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 112. Strength of applicability for the body of evidence evaluating asymptomatic deep vein thrombosis in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of asymptomatic deep vein thrombosis in patients who had total hip replacement surgery	NA	No data
Incidence of asymptomatic deep vein thrombosis in patients who had total knee replacement surgery	NA	No data
Incidence of asymptomatic deep vein thrombosis in patients who had hip fracture surgery	NA	No data
General versus regional anesthesia	Low	There is insufficient data to determine the impact of general versus regional anesthesia on the risk of asymptomatic deep vein thrombosis in patients who had major orthopedic surgery. Data is not applicable to hip replacement surgery. Overall applicability is limited because both studies were conducted outside of the United States and one used anesthetics unavailable in the United States. Additionally primary versus revision surgery was not reported and duration of followup was short.
Tourniquet use versus none	Low	Compared to no use of a tourniquet, those who had surgery with a tourniquet did not have a difference in the risk of asymptomatic deep vein thrombosis. Data is highly applicable to knee replacement surgery although the trial was conducted in the United Kingdom and had a short duration of followup. Data is not applicable to other major orthopedic surgeries.

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had a decrease in the risk of asymptomatic deep vein thrombosis. Data is applicable to primary total hip replacement, has limited applicability to primary knee replacement and no applicability to hip fracture surgery. Applicability is limited due to the short duration of follow up and because all trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of asymptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary hip fracture surgery. Data is not applicable to primary or revision total hip or total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight agents did not have a difference in the risk of asymptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because all trials were conducted outside of the United States. Data is highly applicable to total hip replacement surgery. Applicability is limited based on the type of surgery; primary or secondary. Data is not applicable to primary or revision total knee or hip replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Moderate	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of asymptomatic deep vein thrombosis. Data is moderately applicable to primary total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decreased risk of asymptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the type of surgery (primary versus revision) was not reported. Data is highly applicable to total knee replacement and not applicable to other major orthopedic surgeries.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to, mechanical prophylaxis patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of asymptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because this trial was conducted in the United Kingdom. Data is highly applicable to primary total hip replacement. Data is not applicable to primary or revision total knee or hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the risk of asymptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data has a high applicability to the use of dalteparin in hip fracture surgery and is not applicable in other major orthopedic surgeries.
Intermittent pneumatic compression device by Kendall versus Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Low	Compared with pharmacologic prophylaxis alone, patients who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis did not have a difference in the risk of asymptomatic deep vein thrombosis. Data is highly applicable to patients who had primary total hip replacement and received a sequential pharmacologic therapy of unfractionated heparin for 3 days then aspirin plus the mechanical prophylaxis of venous foot pumps versus the pharmacologic prophylaxis alone. Data is not applicable to other major orthopedic surgeries.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decreased risk of asymptomatic deep vein thrombosis. Data is highly applicable to the use of injectable low molecular weight heparin agents although overall applicability is limited because all trials were conducted outside of the United States. Data has a low level of applicability to oral vitamin K antagonists. Data is highly applicable to primary or revision total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 113. Strength of applicability for the body of evidence evaluating symptomatic deep vein thrombosis in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of symptomatic deep vein thrombosis in patients who had total hip replacement surgery	NA	No data
Incidence of symptomatic deep vein thrombosis in patients who had total knee replacement surgery	NA	No data
Incidence of symptomatic deep vein thrombosis in patients who had hip fracture surgery	NA	No data
General versus regional anesthesia	Low	Compared to patients who received regional anesthesia, those who received general anesthesia did not have a difference in the risk of symptomatic deep vein thrombosis. Data is not applicable to hip replacement surgery. Overall applicability is limited because both studies were conducted outside of the United States and one used anesthetics unavailable in the United States. Additionally primary versus revision surgery was not reported and duration of followup was short.
Tourniquet use versus none	Low	Compared to those who had no tourniquet, patients who had surgery with a tourniquet did not have a difference in the risk of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although the trial was conducted in England. Data is not applicable to other major orthopedic surgeries.
Maintained femoral blood flow versus standard procedure	Low	Compared to standard procedure, patients who had surgery to maintain femoral blood flow did not have a difference in the risk of symptomatic deep vein thrombosis. Overall applicability is limited as this intervention is only for experimentation purposes and the trial was conducted in hip replacement surgery therefore inapplicable to other major orthopedic surgeries.
Impact of metabolic syndrome	Low	Metabolic syndrome increases the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of age	Low	Age does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of education	Low	Education does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.

Comparison	Strength of applicability	Conclusion with description of applicability
Impact of diabetes	Low	Diabetes does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of hypertension	Low	Hypertension does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of hypercholesterolemia	Low	Hypercholesterolemia does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of body mass index	Low	Body mass index does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Impact of comorbidities	Low	Presence of comorbidities does not impact the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although not applicable to the other major orthopedic surgeries. Overall applicability is limited as this study was conducted in Canada.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis did not have a difference in the risk of symptomatic deep vein thrombosis. Data is applicable to primary total hip replacement, has limited applicability to primary knee replacement and no applicability to hip fracture surgery. Applicability is limited due to the short duration of follow up and because all trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of symptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary hip fracture surgery. Data is not applicable to primary or revision total hip or total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight agents did not have a difference in the odds of symptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to total hip replacement surgery. Data is moderately applicable to primary total knee replacement surgery. Applicability is limited based on the type of surgery; primary or secondary. Data is not applicable to primary or revision hip replacement surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Moderate	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of symptomatic deep vein thrombosis. Data is moderately applicable to primary or revision total hip replacement surgery. Data is moderately applicable to revision total knee replacement surgery. Data has a low level of applicability to primary hip fracture surgery and overall is limited because the majority of trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of symptomatic deep vein thrombosis. Overall applicability is limited because the majority of trials were conducted outside of the United States. Data is moderately applicable to primary total knee replacement surgery. Data has a low level of applicability to primary total hip replacement surgery. Data is not applicable to revision total knee, total hip or hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of symptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary or revision total hip replacement surgery and moderate applicable to total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of symptomatic deep vein thrombosis. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee or hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of symptomatic deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression device by Kendall versus Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Low	Compared with pharmacologic prophylaxis alone, patients who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis did not have a difference in the risk of symptomatic deep vein thrombosis. Data is highly applicable to patients who had primary total hip replacement and received a sequential pharmacologic therapy of unfractionated heparin for 3 days then aspirin plus the mechanical prophylaxis of venous foot pumps versus the pharmacologic prophylaxis alone. Data is not applicable to other major orthopedic surgeries.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decreased risk of symptomatic deep vein thrombosis. Data is moderately applicable to the use of injectable low molecular weight heparin agents. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data is highly applicable to primary or revision total hip replacement surgery, has moderate applicability to hip fracture surgery and is not applicable to primary or revision total knee replacement. Overall applicability is limited because all trials were conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 114. Strength of applicability for the body of evidence evaluating proximal deep vein thrombosis in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of proximal deep vein thrombosis in patients who had total hip replacement surgery	Low	The pooled incidence of proximal deep vein thrombosis was 32 percent in patients who had total hip replacement surgery. Overall applicability is limited because all trials were conducted outside of the United States.
Incidence of proximal deep vein thrombosis in patients who had total knee replacement surgery	Low	The pooled incidence of proximal deep vein thrombosis in patients who had total knee replacement surgery was 17 percent. Overall applicability is limited because the majority of data is derived from the study conducted in Singapore while only a small percent (<10 percent) of data is derived from the study conducted in the United States. One trial was published in 2009 while the other in 1980.
Incidence of proximal deep vein thrombosis in patients who had hip fracture surgery	NA	No data
General versus regional anesthesia	Low	Compared to patients who received regional anesthesia, those who received general anesthesia have no difference in the risk of proximal deep vein thrombosis. Data is not applicable to hip fracture surgery. Although trials were conducted in the United States, the majority overall used anesthetics unavailable in the United States, and had a short duration of followup.
Cemented versus cementless arthroplasty	Low	Compared to patients who had cementless arthroplasty, those who had cemented arthroplasty had no difference in the risk of proximal deep vein thrombosis. Data is highly applicable to hip replacement surgery although overall applicability is limited as both trials were conducted outside of the United States and had a short duration of followup. Data is not applicable to knee replacement or hip fracture surgery.
Bone vacuum cement versus standard procedure	Low	Compared to standard procedure, patients who received bone vacuum cement had a lower risk of proximal deep vein thrombosis. Data is highly applicable to primary total knee replacement surgery although overall applicability is limited as the trial was conducted in Germany and had a short duration of followup. Data is not applicable to hip replacement or hip fracture surgery.
Tourniquet use versus none	Low	Compared to those who had no tourniquet, patients who had surgery with a tourniquet did not have a difference in the risk of proximal deep vein thrombosis. Data is highly applicable to primary knee replacement surgery although the trial was conducted in England. Data is not applicable to other major orthopedic surgeries.
Limited time in flexion/dislocation versus standard procedure	Low	Compared to standard procedure, patients whose limb was in flexion and dislocation for a limited time did not have a difference in the risk of proximal deep vein thrombosis. Data is highly applicable to primary hip replacement surgery although the duration of followup was short. Data is not applicable to other major orthopedic surgeries.
Impact of congestive heart failure	Moderate	Congestive heart failure significantly increases the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of age	Moderate	Insufficient data is available to determine the impact of age on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of prior deep vein thrombosis	Moderate	Prior deep vein thrombosis has no impact on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Impact of inactive malignancy	Moderate	Inactive malignancy has no impact on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of current hormone replacement therapy	Moderate	Current hormone replacement therapy has no impact on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of chronic tobacco use	Moderate	Chronic tobacco use has no impact on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Impact of blood disorders	Moderate	Presence of blood disorders has no impact on the odds of proximal deep vein thrombosis. Data is highly applicable to hip or knee replacement surgery although not applicable to hip fracture surgery.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had a decrease in the risk of proximal deep vein thrombosis. Data is highly applicable to hip replacement surgery, moderately applicable to knee replacement surgery and not applicable to hip fracture surgery. Data is not applicable to revision surgery. Applicability is limited due to the short duration of follow up and because all trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received mechanical prophylaxis did not have a difference in the risk of proximal deep vein thrombosis. Data is highly applicable to patients receiving prophylaxis with venous foot pump undergoing primary total hip replacement but not applicable to total hip replacement or hip fracture surgery. Applicability is limited due to the short duration of follow up and because the one available trial was conducted outside of the United States.
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the risk of proximal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is moderately applicable to primary or revision total knee or total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of proximal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Applicability is limited because data is only available for bilateral total knee replacement. Data has a low level of applicability to bilateral total knee replacement. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decreased risk of proximal deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States. Applicability is limited based on the type of surgery; primary or revision. Data is moderately applicable to total hip replacement surgery. Data has a low level of applicability to total knee and hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increase in the odds of proximal deep vein thrombosis. Applicability is limited by the duration of follow up. Data has moderate applicability to primary or revision total hip replacement surgery. Data has a low level of applicability to primary hip fracture surgery and revision total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Moderate	Compared to injectable or oral direct thrombin, patients who had major orthopedic surgery and received inhibitors injectable low molecular weight heparin agents did not have a difference in the risk of proximal deep vein thrombosis. Applicability is limited by the duration of follow up. Data is moderately applicable to primary total knee or total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of proximal deep vein thrombosis. Applicability is limited by the short duration of follow up. Data is highly applicable to primary and revision total hip and total knee or hip replacement surgery and is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of proximal deep vein thrombosis. Data is moderately applicable to primary total hip replacement surgery. Data has a low level of applicability to primary total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery and is limited overall because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable unfractionated heparin agents had an increase in the odds of proximal deep vein thrombosis. Data is moderately applicable to primary total hip and total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery and is limited overall because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists had a decrease in the risk of proximal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary or revision total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the risk of proximal deep vein thrombosis. Data has a low level of applicability to primary total hip replacement surgery and primary hip fracture surgery. Data is not applicable to primary or revision total knee replacement surgery. Applicability is limited because the trials were conducted outside of the United States

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression device by Kendall versus Venaflow intermittent pneumatic compression device	Low	Compared to prophylaxis with the Venaflow intermittent pneumatic compression device, patients who had major orthopedic surgery and received the device by Kendall had no difference in the odds of proximal deep vein thrombosis. Data is moderately applicable to primary or revision total hip replacement surgery. Data is moderately applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	Moderate	Compared to prophylaxis with intermittent pneumatic compression devices, patients who had major orthopedic surgery and received prophylaxis with graduated compression stockings did not have a difference in the odds of proximal deep vein thrombosis. Data is moderately applicable to primary and revision total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Moderate	Compared with pharmacologic prophylaxis alone, patients who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis did not have a difference in the risk of proximal deep vein thrombosis. Applicability is limited due to the short duration of followup. Data is highly applicable to both primary total hip and knee replacement surgery although not applicable to hip fracture surgery or revision surgery.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	Low	Compared with pharmacologic prophylaxis alone, the hips of patients which underwent replacement surgery and received pharmacologic plus mechanical prophylaxis did not have a difference in the risk of proximal deep vein thrombosis. Applicability is limited because only one trial was available. Applicability is high for primary or revision total hip replacement surgery although not applicable to other major orthopedic surgeries.
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had a decreased risk of proximal deep vein thrombosis. Data is highly applicable to primary hip replacement surgery with the use of injectable low molecular weight heparin agents. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data has a moderate level of applicability to hip fracture surgery and a low level of applicability to total knee replacement surgery. Overall applicability is limited because the majority of trials were conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=not applicable

Table 115. Strength of applicability for the body of evidence evaluating distal deep vein thrombosis in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of distal deep vein thrombosis in patients who had total hip replacement surgery	Low	The pooled incidence of distal deep vein thrombosis in patients who had total hip replacement surgery was 30 percent. Overall applicability is limited because both trials were conducted outside of the United States and one was published in 2009 while the other in 1980.
Incidence of distal deep vein thrombosis in patients who had total knee replacement surgery	Low	The pooled incidence of distal deep vein thrombosis in patients who had total knee replacement surgery was 22 percent. Overall applicability is limited because the majority of data is derived from the study conducted in Singapore while only a small percent (<10 percent) of data is derived from the study conducted in the United States. One trial was published in 2009 while the other in 1980.
Incidence of distal deep vein thrombosis in patients who had hip fracture surgery	NA	No data
General versus regional anesthesia	Low	There was insufficient evidence to determine the impact of general versus regional anesthesia on the risk of distal deep vein thrombosis. Data is not applicable to hip fracture surgery. Overall applicability is limited because the majority of data is derived from trials conducted outside of the United States using agents that are currently not available in the United States.
Cemented versus cementless arthroplasty	Low	Compared to patients who had cementless arthroplasty, those who had cemented arthroplasty had no difference in the risk of distal deep vein thrombosis. Data is highly applicable to hip replacement surgery although overall applicability is limited as both trials were conducted outside of the United States and had a short duration of followup. Data is not applicable to knee replacement or hip fracture surgery.
Bone vacuum cement versus standard procedure	Low	Compared to standard procedure, patients who received bone vacuum cement did not have a difference in the risk of distal deep vein thrombosis. Data is highly applicable to primary total knee replacement surgery although overall applicability is limited as the trial was conducted in Germany and had a short duration of followup. Data is not applicable to hip replacement or hip fracture surgery.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had a decrease in the risk of distal deep vein thrombosis. Data is highly applicable to primary total hip replacement, moderately applicable to total knee replacement and not applicable to hip fracture surgery. Applicability is limited by the short duration of follow up and because all of the trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received mechanical prophylaxis had no difference in the risk of distal deep vein thrombosis. Data is highly applicable to patients receiving prophylaxis with venous foot pump undergoing primary total hip replacement but not applicable to total hip replacement or hip fracture surgery. Applicability is limited due to the short duration of follow up and because the one available trial was conducted outside of the United States.
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral antiplatelet agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral antiplatelet agents had an increase in the risk of distal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Applicability is limited because data is only available for bilateral total knee replacement. Data has a low level of applicability to bilateral total knee replacement. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of distal deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the majority of trials were conducted outside of the United States. Applicability is limited based on the type of surgery; primary or revision. Data is moderately applicable to total hip replacement surgery. Data has a low level of applicability to total knee and hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increased risk of distal deep vein thrombosis. Applicability is limited by the duration of follow up. Data has moderate applicability to total hip replacement surgery. Data has a low level of applicability to primary hip fracture surgery and revision total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decreased risk of distal deep vein thrombosis. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decreased risk of distal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Data is highly applicable to primary total hip or knee replacement surgery although is not applicable to revision surgery or hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of distal deep vein thrombosis. Data is moderately applicable to primary total hip replacement surgery. Data has a low level of applicability to primary total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery and overall is limited because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists did not have a difference in the odds of distal deep vein thrombosis. Applicability is limited due to the short duration of follow up. Applicability is limited because the type of surgery; primary or revision was not reported. Data is moderately applicable to total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of distal deep vein thrombosis. Applicability is limited due to the short duration of follow up and because the trials were conducted outside of the United States. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	Low	Compared to prophylaxis with the intermittent pneumatic compression device by Kendal, patients who had major orthopedic surgery and received the Venaflow device had a decreased risk of distal deep vein thrombosis. Data is moderately applicable to primary or revision total hip replacement surgery. Data is moderately applicable to primary or revision total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	Moderate	Compared to graduated compression stockings, patient who had major orthopedic surgery and received intermittent pneumatic compression devices had a decreased risk of distal deep vein thrombosis. Data is highly applicable to the Venaflow intermittent pneumatic compression device and Comprinet Pro graduated compression stockings. Data is highly applicable to total hip or knee replacement surgery but is not applicable to hip fracture surgery.
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	Low	Compared with pharmacologic prophylaxis alone, patients who had major orthopedic surgery and received pharmacologic plus mechanical prophylaxis did not have a difference in the risk of distal deep vein thrombosis. Applicability is limited because only one trial was available comparing enoxaparin plus IPC versus enoxaparin alone and the duration of followup was short. Data is highly applicable to total hip or knee replacement surgery and not applicable to hip fracture surgery.
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the risk of distal deep vein thrombosis. Data is highly applicable to primary hip replacement surgery with the use of injectable low molecular weight heparin agents. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data has a moderate level of applicability to hip fracture surgery and a low level of applicability to total knee replacement surgery. Overall applicability is limited because the majority of trials were conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=not applicable

Table 116. Strength of applicability for the body of evidence evaluating major bleeding in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of major bleeding in patients who had total hip replacement surgery	Low	The pooled incidence of major bleeding in patients who had total hip replacement surgery was 1 percent. Overall applicability is limited because 4 of the 5 trials were conducted outside of the United States and the trial conducted in the United States contributed a small percent of the overall population (17 percent).
Incidence of major bleeding in patients who had total knee replacement surgery	Low	The pooled incidence of major bleeding in patients who had total knee replacement surgery was 3 percent. Overall applicability was limited because both trials were conducted in Japan.
Incidence of major bleeding in patients who had hip fracture surgery	Low	Based on one trial, the incidence of major bleeding in patients who had hip fracture surgery was 8 percent. Overall applicability is limited because this trial was conducted in Canada and published in 1989.
General versus regional anesthesia	Low	There was insufficient evidence to determine the impact of general versus regional anesthesia on the risk of major bleeding. Data is highly applicable to primary hip replacement surgery although overall applicability is limited because the trial was conducted in France using agents that are currently not available in the United States.
Impact of age	Moderate	There was insufficient evidence to determine the impact of age on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Impact of obesity	Moderate	There was insufficient evidence to determine the impact of obesity on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Impact of gender	Moderate	There was insufficient evidence to determine the impact of gender on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Impact of risk of bleeding	Moderate	There was insufficient evidence to determine the impact of the risk of bleeding on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Impact of surgical procedure	Moderate	There was insufficient evidence to determine the impact of the surgical procedure on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Impact of prophylaxis agent used	Moderate	There was insufficient evidence to determine the impact of the prophylaxis agent used on the risk of major bleeding. Data is applicable to all three major orthopedic surgeries, although the single trial was conducted in Belgium.
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had no difference in the risk of major bleeding. Data is highly applicable to primary hip replacement surgery, moderately applicable to primary knee replacement and hip fracture surgery. Applicability is limited because the majority of trials were conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the risk of major bleeding. Applicability is limited because the type of surgery; primary or revision was not reported. Data is moderately applicable to hip fracture surgery. Data is not applicable to primary or revision total knee or total hip replacement surgery.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decrease in the odds of major bleeding. Applicability is limited because the type of surgery; primary or revision was not reported. Data is highly applicable to total hip replacement surgery. Data has a low level of applicability to total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decrease in the odds of major bleeding. Data has moderate applicability to primary or revision total hip replacement surgery. Data has a low level of applicability to primary hip fracture surgery and revision total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of major bleeding. Applicability is limited because the majority of trials were conducted outside of the United States. Data is moderately applicable to primary total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared to oral vitamin K antagonists patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increase in the odds of major bleeding. Applicability is limited by the type of surgery; primary or revision. Data is highly applicable to total hip and total knee replacement surgery and not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	Moderate	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable unfractionated heparin agents had an increase in the odds of major bleeding. Applicability is limited because the type of surgery; primary or revision was not reported. Data is moderately applicable to total hip replacement, total knee replacement and hip fracture surgery.
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the risk of major bleeding. Data has a low level of applicability to primary total hip replacement surgery and primary hip fracture surgery. Data is not applicable to primary or revision total knee replacement surgery. Applicability is limited because the trials were conducted outside of the United States
Intermittent pneumatic compression device by Kendal versus the Venaflo intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the odds of major bleeding. Data is moderately applicable to the use of injectable low molecular weight heparin agents. Data has a low level of applicability to oral vitamin K antagonists and injectable factor Xa inhibitors. Data is highly applicable to primary total hip replacement surgery, moderately applicable to hip fracture surgery and has low applicability to hip fracture surgery. Overall applicability is limited because the majority of trials were conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 117. Strength of applicability for the body of evidence evaluating major bleeding leading to reoperation in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
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Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of major bleeding leading to reoperation in patients who had total hip replacement surgery	Moderate	Based on two trials the incidence of major bleeding leading to reoperation was 0 percent in patients who had total hip replacement surgery. Overall applicability is limited moderate because the majority of data is derived from a study conducted in the United States although this trial was published in 1992 while the second trial was published in 1997.
Incidence of major bleeding leading to reoperation in patients who had total knee replacement surgery	Low	Based on one trial, the incidence of major bleeding leading to reoperation was 0 percent. Overall applicability is limited because the trial was conducted in Japan.
Incidence of major bleeding leading to reoperation in patients who had hip fracture surgery	NA	No data
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had no difference in the risk of major bleeding leading to reoperation. Data is highly applicable to primary total knee and hip replacement and total knee replacement. Data is not applicable to hip fracture surgery. Applicability is limited because all trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of major bleeding leading to reoperation. Data has moderate applicability to primary or revision total hip replacement surgery. Data has a low level of applicability to primary hip fracture surgery and revision total knee replacement surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of major bleeding leading to reoperation. Data is moderately applicable to primary total knee replacement surgery. Data has a low level of applicability to primary total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery and is limited because the trials were conducted outside of the United States.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of major bleeding leading to reoperation. Data is moderately applicable to primary total knee replacement surgery and is not applicable to other major orthopedic surgeries.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of major bleeding leading to reoperation. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery and has limited applicability because the trials were conducted outside of the United States.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the odds of major bleeding leading to reoperation. Data is highly applicable to the use of injectable factor Xa inhibitors and hip fracture surgery. Data is not applicable to injectable low molecular weight heparin agents or oral vitamin K antagonists or to primary or revision total hip replacement or total knee replacement surgery. Overall applicability is limited because the trial was conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 118. Strength of applicability for the body of evidence evaluating minor bleeding in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of minor bleeding in patients who had total hip replacement surgery	Moderate	The pooled incidence of minor bleeding in patients who had total hip replacement surgery was 6 percent. Overall applicability is moderate as half of the data is derived from trials conducted in the United States. Two trials were published in the 90's, two in the 80's and one in 2008.
Incidence of minor bleeding in patients who had total knee replacement surgery	Low	The pooled incidence of minor bleeding in patients who had total knee replacement surgery was 6 percent. Overall applicability was limited because both trials were conducted in Japan.
Incidence of minor bleeding in patients who had hip fracture surgery	NA	No data
Bone vacuum cement versus standard procedure	Low	Compared to standard procedure, patients who received bone vacuum cement did not have a difference in the risk of minor bleeding. Data is highly applicable to primary total knee replacement surgery although overall applicability is limited as the trial was conducted in Germany and had a short duration of followup. Data is not applicable to hip replacement or hip fracture surgery.
Pharmacologic prophylaxis versus no prophylaxis	Moderate	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had an increase in the risk of minor bleeding. Data is highly applicable to primary total knee and hip replacement and total knee replacement. Data is not applicable to hip fracture surgery. Applicability is limited because all of the trials were conducted outside of the United States.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin did not have a difference in the risk of minor bleeding. Applicability is limited because the type of surgery; primary or revision was not reported and because the majority of trials were conducted outside of the United States. Data is moderately applicable to total hip replacement surgery. Data has a low level of applicability to total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared with injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had a decrease in the odds of minor bleeding. Data is highly applicable to revision surgery for total knee replacement and total hip replacement surgery. Although the one trial evaluating hip replacement was conducted in Japan. Data is not applicable to hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in risk of minor bleeding. Applicability is limited because the majority of trials were conducted outside of the United States. Data is moderately applicable to primary total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Moderate	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin had an increased risk of minor bleeding. Data is highly applicable to primary or revision total hip or knee replacement surgery although is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists did not have a difference in the odds of minor bleeding. Applicability is limited due to the type of surgery; primary or revision. Data is highly applicable to total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of minor bleeding. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery. Applicability is limited because the trials were conducted outside of the United States
Intermittent pneumatic compression device by Kendal versus the Venaflo intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Moderate	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had an increase in the odds of minor bleeding. Data has a low level of applicability to the use of injectable factor Xa inhibitors. Data is highly applicable to injectable low molecular weight heparin agents. And primary or revision hip replacement surgery. Data is not applicable to the use of oral vitamin K antagonists or to knee replacement surgery. Data has a moderate level of applicability to hip fracture surgery. Overall applicability is limited because the majority of trials were conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 119. Strength of applicability for the body of evidence evaluating surgical site bleeding in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of surgical site bleeding in patients who had total hip replacement surgery	NA	No data
Incidence of surgical site bleeding in patients who had total knee replacement surgery	NA	No data
Incidence of surgical site bleeding in patients who had hip fracture surgery	NA	No data
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received oral antiplatelet agents did not have a difference in the odds of surgical site bleeding. Applicability is limited due to the type of surgery; primary or revision. Data is highly applicable to total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received low molecular weight heparin agents did not have a difference in the odds of surgical site bleeding. Applicability is limited because the type of surgery; primary or revision was not reported. Data is moderately applicable to total hip replacement surgery. Data has a low level of applicability to total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odd of surgical site bleeding. Applicability is limited because the trial was conducted outside of the United States. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin, patients who had major orthopedic surgery and received inhibitors injectable low molecular weight heparin agents had an increased risk of surgical site bleeding. Data is highly applicable to primary total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents had an increase in the odds of surgical site bleeding. Data is highly applicable to primary total hip or knee replacement surgery and is not applicable to revision surgery or hip fracture surgery.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable or oral direct thrombin inhibitors, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of surgical site bleeding. Applicability is limited because the trial was conducted outside of the United States. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of surgical site bleeding. Applicability is limited due to the type of surgery; primary or revision and because the trials were conducted outside of the United States. Data is highly applicable to total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis had an increase in the odds of surgical site bleeding. Data is highly applicable to the use of injectable factor Xa inhibitors and hip fracture surgery. Data is not applicable to injectable low molecular weight heparin agents or oral vitamin K antagonists or to primary or revision total hip replacement or total knee replacement surgery. Overall applicability is limited because the trial was conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 120. Strength of applicability for the body of evidence evaluating bleeding leading to infection in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of surgical site bleeding in patients who had total hip replacement surgery	NA	No data
Incidence of surgical site bleeding in patients who had total knee replacement surgery	NA	No data
Incidence of surgical site bleeding in patients who had hip fracture surgery	NA	No data
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus intermittent pneumatic compression devices	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 121. Strength of applicability for the body of evidence evaluating bleeding leading to transfusion in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Incidence of bleeding leading to transfusion in patients who had total hip replacement surgery	Moderate	Based on one trial, the incidence of bleeding leading to transfusion was 0 percent in patients who had total hip replacement surgery. Overall applicability was limited because the trial was conducted in 1992.
Incidence of bleeding leading to transfusion in patients who had total knee replacement surgery	Low	Based on one trial, the incidence of bleeding leading to transfusion was 0 percent in patients who had total knee replacement surgery. Overall applicability was limited because the trial was conducted in Japan.
Incidence of bleeding leading to transfusion in patients who had hip fracture surgery	NA	No data
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had no difference in the odds of bleeding leading to transfusion. Data is highly applicable to the use of dabigatran in primary total knee replacement surgery. Data is not applicable to total hip replacement or hip fracture surgery. Applicability is limited because the one trial available was conducted in Japan.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of bleeding leading to transfusion. Data is moderately applicable to primary total knee replacement and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery and is limited because the trials were conducted outside of the United States.
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to oral vitamin K antagonists, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the odds of bleeding leading to transfusion. Data is moderately applicable to primary total hip replacement surgery and is not applicable to other major orthopedic surgeries.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did had a difference in the odds of bleeding leading to transfusion. Data is highly applicable to the use of injectable factor Xa inhibitors and hip fracture surgery. Data is not applicable to injectable low molecular weight heparin agents or oral vitamin K antagonists or to primary or revision total hip replacement or total knee replacement surgery. Overall applicability is limited because the trial was conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 122. Strength of applicability for the body of evidence evaluating heparin induced thrombocytopenia in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin, patients who had major orthopedic surgery and received injectable low molecular weight heparin had a decrease in the odds of heparin induced thrombocytopenia. Applicability is limited because the type of surgery; primary or revision is not reported. Data is highly applicable to total hip replacement surgery. Data is moderately applicable to total knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	Low	Compared to other low molecular weight heparin agents, patients who had major orthopedic surgery and received enoxaparin did not have a difference in the odds of heparin induced thrombocytopenia. Data is highly applicable to the use of tinzaparin in primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery. Applicability is limited because the trials were conducted outside of the United States
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 123. Strength of applicability for the body of evidence evaluating discomfort in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	NA	No data
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received low molecular weight heparin agents had a decreased risk of discomfort. Applicability is limited because the trial was conducted outside of the United States. Data is highly applicable to primary total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	NA	No data
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 124. Strength of applicability for the body of evidence evaluating readmission in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had no difference in the rate of readmission. Data is highly applicable to the use of warfarin in primary total knee replacement surgery. Data is not applicable to total hip replacement or hip fracture surgery.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	Low	Compared to injectable unfractionated heparin patients who had major orthopedic surgery and received low molecular weight heparin agents did not have a difference in the risk of readmission. Data is highly applicable to primary or revision total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	NA	No data
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	NA	No data
Injectable low molecular weight heparin agents versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of readmission. Applicability is limited because the trials were conducted outside of the United States. Data is moderately applicable to primary total knee and total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery.
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	Low	Compared to mechanical prophylaxis, patients who had major orthopedic surgery and received oral vitamin K antagonists did not have a difference in the odds of readmission. Data is highly applicable to primary or revision total hip replacement surgery. Data is not applicable to primary or revision total knee replacement or hip fracture surgery.
Enoxaparin versus other low molecular weight heparin agents	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the risk of readmission. Data is highly applicable to the use of injectable low molecular weight heparin agents in primary total hip or knee replacement surgery. Data is not applicable to primary or revision hip fracture surgery. Data is not applicable to revision total knee or total hip replacement surgery.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Table 125. Strength of applicability for the body of evidence evaluating reoperation in patients who had major orthopedic surgery

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic prophylaxis versus no prophylaxis	Low	Compared to no prophylaxis, patients who had major orthopedic surgery and received pharmacologic prophylaxis had an increase in the rate of reoperation. Data is highly applicable to the use of warfarin in primary total knee replacement surgery. Data is not applicable to total hip replacement or hip fracture surgery.
Mechanical prophylaxis versus no prophylaxis	NA	No data
Oral antiplatelet agents versus oral vitamin K antagonists	NA	No data
Oral antiplatelet agents versus mechanical prophylaxis	NA	No data
Injectable low molecular weight heparin agents versus injectable unfractionated heparin	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors	Low	Compared to injectable or oral factor Xa, patients who had major orthopedic surgery and received inhibitors injectable low molecular weight heparin agents did not have a difference in the risk of reoperation. Applicability is limited because the trial was conducted outside of the United States. Data is highly applicable to revision total knee replacement surgery. Data is not applicable to primary or revision total hip replacement or hip fracture surgery.
Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable low molecular weight heparin agents versus oral vitamin K antagonists	Low	Compared to, oral vitamin K antagonists patients who had major orthopedic surgery and received injectable low molecular weight heparin agents did not have a difference in the risk of reoperation. Data is moderately applicable to primary total knee replacement surgery and is not applicable to other major orthopedic surgeries.
Injectable low molecular weight heparin agents versus mechanical prophylaxis	NA	No data
Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors	NA	No data
Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors	NA	No data
Injectable unfractionated heparin versus mechanical prophylaxis	NA	No data
Oral vitamin K antagonists versus mechanical prophylaxis	NA	No data
Enoxaparin versus other low molecular weight heparin agents	NA	No data
Intermittent pneumatic compression device by Kendal versus the Venaflow intermittent pneumatic compression device	NA	No data
ActiveCare intermittent pneumatic compression device versus Flowtron intermittent pneumatic compression device	NA	No data
Intermittent pneumatic compression versus graduated compression	NA	No data
Pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis	NA	No data

Comparison	Strength of applicability	Conclusion with description of applicability
Pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis	NA	No data
Effect of prolonging prophylaxis for 28 days compared to prophylaxis for 7 to 10 days	Low	Compared to 7 to 10 days of prophylaxis, patients who had major orthopedic surgery and received 28 days or more of prophylaxis did not have a difference in the risk of reoperation. Data is highly applicable to the use of injectable low molecular weight heparin agents in primary or revision total hip replacement surgery. Data is not applicable to primary or revision hip fracture surgery or total knee replacement surgery. Overall applicability is limited because the trial was conducted outside of the United States.
Inferior vena cava filter versus mechanical prophylaxis	NA	No data

Abbreviations: NA=Not applicable

Appendix J. Glossary

Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.

Deep Venous Thrombosis (DVT): A blood clot occurring in a leg vein and verified with Doppler ultrasound or venography. Proximal deep vein thrombosis was defined as blood clot occurring in either popliteal, femoral, or any deep veins of the pelvis. Distal vein thrombosis was defined as blood clot occurring distal to the popliteal vein in the calf veins of the leg. When both bilateral and unilateral clots data were available, unilateral clots data was used for the analysis.

DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.

Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.

Hip Fracture Surgery (HFS): The surgical procedure to treat hip fracture.

I²: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

Major Orthopedic Surgery: Total hip arthroplasty, total knee arthroplasty, hip fracture surgery.

Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.

Other Orthopedic Surgery: Knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or discectomy all of the lumbar region).

Peto's Odds Ratio (OR): An odds ratio is the ratio of an event occurring in an exposed group to an event occurring in the nonexposed group in a given population. A ratio of one indicates no difference in the odds between the two groups. Peto's odds ratios are used to compare two groups when the number of events is rare.

Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.

Pulmonary Embolism (PE): A blood clot in the vasculature of the lung. In order to have a pulmonary embolism in our review, it needed to be verified with spiral computed tomography angiography or ventilation/perfusion scan with either Prospective Investigation of Pulmonary

Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for pulmonary embolism.

Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a nonexposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.

Sensitivity Analyses: A “what if” analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.

Standard Deviations (SDs): A measure of the variability of a dataset. For a simple dataset with numbers, can be calculated using the following formula: $\sigma = ((\sum(x-x_m))^2/N)^{0.5}$ where σ is standard deviation, x_m is the average, $\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x , N is the total number of values.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis.

Total Hip Arthroplasty (THR): The surgical replacement of the hip.

Total Knee Arthroplasty (TKA): The surgical replacement of the knee.

Venous Thromboembolism (VTE): The occurrence of either a deep venous thrombosis or pulmonary embolism.