Comparative Effectiveness Review
Number 191

Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

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This report is based on research conducted by the Brown Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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 can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input 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 email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In conducting a surveillance of the literature since the prior AHRQ report on venous thromboembolism prophylaxis in orthopedic surgery, we consulted several technical, content, and clinical experts. The Technical Experts provided comments on their interpretation of the current state of the evidence and of clinical questions that are currently pertinent to patient management and decisionmaking. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, we sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

Structured Abstract

Background. Major orthopedic surgeries, such as total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgery, carry a high risk for venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE).

Methods. Updating a 2012 review, we compare interventions to prevent VTE after TKR, THR, and HFx surgery. We searched four databases and other sources through June 3, 2016, for randomized controlled trials (RCTs) and large nonrandomized comparative studies (NRCSs) reporting postoperative VTE, major bleeding, and other adverse events. We conducted pairwise meta-analyses, Bayesian network meta-analyses, and strength of evidence (SoE) synthesis.

Results. Overall, 127 RCTs and 15 NRCSs met criteria. For THR: low molecular weight heparin (LMWH) has lower risk than unfractionated heparin (UFH) of various VTE outcomes (moderate to high SoE) and major bleeding (moderate SoE). LMWH and aspirin have similar risks of total PE, symptomatic DVT, and major bleeding (low SoE). LMWH has less major bleeding (low SoE) than direct thrombin inhibitors (DTI), but DTI has lower DVT risks (moderate SoE). LMWH has less major bleeding than vitamin K antagonists (VKA) (high SoE). LMWH and factor Xa inhibitor (FXaI) comparisons are inconsistent across VTE outcomes, but LMWH has less major bleeding (high SoE). VKA has lower proximal DVT risk than mechanical devices (high SoE). Longer duration LMWH has lower risk of various VTE outcome risks (low to high SoE). Higher dose LMWH has lower total DVT risk (low SoE) but more major bleeding (moderate SoE). Higher dose FXaI has lower total VTE risk (low SoE). For TKR: LMWH has lower DVT risks than VKA (low to high SoE), but VKA has less major bleeding (low SoE). FXaI has lower risk than LMWH of various VTE outcomes (low to moderate SoE), but LMWH has less major bleeding (low SoE) and more study-defined serious adverse events (low SoE). Higher dose DTI has lower DVT risk (moderate to high SoE) but more major bleeding (low SoE). Higher dose FXaI has lower risk of various VTE outcomes (low to moderate SoE). For HFx surgery: LMWH has lower total DVT risk than FXaI (moderate SoE).

Conclusions. VTE prophylaxis after major orthopedic surgery trades off lowered VTE risk with possible adverse events—in particular, for most interventions, major bleeding. In THR, LMWH has lower VTE and adverse event risks than UFH, LMWH and aspirin have similar risks of VTE and major bleeding, DTI has lower DVT risk than LMWH but higher major bleeding risk, and higher dose LMWH has lower DVT risk but higher major bleeding risk than lower dose. In TKR, VKA has higher DVT risk than LMWH but lower major bleeding risk, and higher dose DTI has lower DVT risk but higher major bleeding risk than lower dose. In HFx surgery and for other intervention comparisons, there is insufficient evidence to assess both benefits and harms, or findings are inconsistent. Importantly, though, most studies evaluate “total DVT” (an outcome of unclear clinical significance since it includes asymptomatic and other low-risk DVTs), but relatively few studies evaluate PE and other clinically important outcomes. This limitation yields a high likelihood of selective outcome reporting bias. There is also relatively sparse evidence on interventions other than LMWH.

Contents

Tables

Figures

Appendixes

Executive Summary

Introduction

Major orthopedic surgery carries a high risk for venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] The major orthopedic surgeries of greatest concern include total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries. PE, an obstruction of a pulmonary artery or its branches usually by an embolic thrombus, is potentially life-threatening and can result in chronic complications with generally poor prognosis, such as thromboembolic pulmonary hypertension.[2-4] DVTs are the principal intermediate process necessary for surgery-related PE and increase the risk of PE.[5] In addition, about 5 to 10 percent of patients with symptomatic DVTs develop severe postthrombotic syndrome, which may include venous ulcers, intractable edema, and chronic pain; although, these outcomes may take 10 years or more to develop.[6] Estimates suggest that in current practice about 4.7 percent of patients undergoing major orthopedic surgery would have symptomatic VTE without prophylaxis.[1] Although, the rate of postoperative VTE is decreasing over time, likely due in part to a combination of more universal thromboprophylaxis and increasing use of early mobilization and decreased used of postoperative narcotics.

A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical devices.[1] Pharmacologic prophylactic treatments include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), antithrombin III-mediated selective factor Xa inhibitors, direct factor Xa inhibitors (FXaI), bivalent and univalent direct thrombin inhibitors (DTI), and antiplatelet agents (such as aspirin). Mechanical prophylaxis aims to minimize stasis, the principal putative factor resulting in venous thrombosis; it may also stimulate fibrinolysis, another mechanism to limit thrombosis. It can be dynamic and intermittent (e.g., intermittent pneumatic compression device [IPC]) or static (e.g., graduated compression stockings [GCS]). The modalities can be used alone or in combination, at variable doses (of drugs) or regimens (of mechanical devices; e.g., different pressure or compression frequency), and for different durations. However, prophylaxis with pharmacologic strategies also has important potential harms (risks) including major bleeding, prosthetic joint infections, and the need for reoperation, which may all lead to major morbidities, death, permanent removal of the prosthetic joint, and increased hospital length of stay and costs.[7] Postoperative bleeding and hematoma formation are considered direct risk factors for the development of prosthetic joint infections.[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. Mechanical devices (when used alone), however, are thought to be inferior to pharmacological agents to prevent VTE.

VTE prophylaxis (or "thromboprophylaxis") is now standard of care for patients undergoing lower extremity major orthopedic surgery. Prophylaxis has been demonstrated to reduce the incidence of symptomatic and asymptomatic DVT (in comparison to placebo or no prophylaxis); however, because of rarity of postoperative PE,[1] the body of randomized controlled trial (RCT) evidence is not adequately powered to demonstrate the effect of prophylaxis on PE. The effect of prophylaxis on DVT risk reduction is generally considered an adequate proxy for likely PE risk reduction, but it remains unknown to what extent reducing the incidence of DVTs impacts the magnitude of any reduction in the incidence of PEs. This is particularly true for "total" DVT, which includes both symptomatic and asymptomatic, and both distal and proximal, DVTs.

Asymptomatic DVTs can be found only with diagnostic testing, which is done routinely only in the research study setting. The link between distal or asymptomatic DVTs and PEs is unclear. Nevertheless, avoiding DVT is a clinically worthwhile goal to reduce the incidence of lower extremity venous disease,[9] such as postphlebitic syndrome, venous insufficiency,[10, 11] and phlegmasia cerulean dolens (resulting in edema, pain, and gangrene).[12]

Scope

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery[13] (hereafter "the 2012 VTE report") addressed many of the uncertainties in this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing THR, TKR, or HFx surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in nonmajor orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 VTE report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence (SoE) that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical prophylaxis reduced the risk of VTE, including, specifically, DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical devices) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new FXaIs. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

We conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 VTE report. The surveillance review is summarized in the online protocol for this review.[14] Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 Agency for Healthcare Research and Quality (AHRQ) report would be of greatest value. Based on their input and the findings of the surveillance review, we focused the update on comparisons between specific prophylaxis interventions; different classes of intervention; different doses, regimens, and treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

The objectives for the systematic review are to update the 2012 VTE report focused on the comparative effectiveness (for VTE outcomes and harms) of different thromboprophylaxis interventions for patients undergoing major orthopedic surgery (THR, TKR, and HFx surgery).

Key Questions

The following are the Key Questions (KQs) addressed by the review:

KQ 1 (update of original KQ 5): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 2 (update of original KQ 6): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual thromboprophylaxis interventions within classes (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 3 (new KQ based on original KQ 8): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 4 (update of original KQ 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 5 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

5.1: What are the comparative effects of different classes of thromboprophylaxis interventions?

5.2: What are the comparative effects of different individual thromboprophylaxis interventions?

KQ 6 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Methods

The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature, using established methodologies as outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[15]

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the KQs that have been published since the 2012 VTE report, which included studies published from 1980 through May 2011. We searched PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and Embase® databases. Searches were limited to January 2010 through June 3, 2016. We included an overlap of more than 1 year with the search done for the 2012 VTE report. The updated literature searches replicated the searches from the 2012 VTE report and added additional terms for new treatments (e.g., factor Xa inhibitors [FXaI]). The search strategy was peer reviewed by an independent, experienced information specialist/librarian.

We also searched the ClinicalTrials.gov registry and the Food and Drug Administration, Healthy Canadians, and the U.K. Medicines & Healthcare products Regulatory Agency Web sites for relevant documents from 2011 through July 18, 2016. In addition, the reference lists of published clinical practice guidelines, systematic reviews, and Scientific Information Packages from manufacturers were hand-searched, and the Technical Expert Panel (TEP) members were invited to provide references of new studies. Existing systematic reviews were used primarily as sources of new studies. With the exception of studies included in the 2012 VTE report, we extracted and incorporated any studies *de novo* and did not summarize or incorporate the existing systematic reviews. All articles identified through these sources were screened for eligibility using the same criteria as was used for articles identified through literature searches.

All studies cited and tabulated in the 2012 VTE report were screened for eligibility on a par with new studies. However, as noted below, we relied on the summary tables in the 2012 VTE report for data from these studies.

Study Eligibility Criteria

The eligibility criteria for this update are mostly similar to the criteria used in the 2012 VTE report, as pertain to updated KQs.

Populations of Interest

For all KQs, studies of patients undergoing major orthopedic surgery (THR, TKR, HFx) were eligible. In contrast with the 2012 VTE report, we excluded studies that included more than one type of surgery but did not report results separately by surgery type. We did not exclude studies based on details regarding the type of eligible surgery, related anesthesia management, or perioperative care. Therefore, for example, both primary and revision arthroplasty and unicompartmental and tricompartmental TKR are included. Subpopulations of interest included those defined by specific surgery, age, race/ethnicity, health status, comorbidities, prior history of abnormal surgical bleeding or bleeding disorder, prior medications (e.g., antiplatelet drugs), kidney function, and treatment adherence/compliance.

Interventions of Interest

The interventions of interest for all KQs included pharmacological VTE prophylaxis agents within the defined classes of antiplatelet agents, low molecular weight heparin (LMWH), unfractionated heparin (UFH), factor VIII inhibitors (FEI), factor Xa inhibitors (FXaI), factor XI inhibitors (FXIi), direct thrombin inhibitors (DTI), vitamin K antagonists (VKA), and mechanical VTE prophylaxis devices within the classes graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC), and venous foot pumps (VFP). We also included studies of prophylactic inferior vena cava filters for KQs 1 and 5 (that compared classes of interventions). We included multimodality therapies KQ 3 (different doses, regimens, or treatment durations). We included studies of combination therapies (e.g., drug plus mechanical device) for KQs 4 and 5 and of different starting times relative to surgery for KQ 6.

Comparators of Interest

We included any of the above interventions as comparators as pertinent, including

- KQ 1 intervention in a different class
- KQ 2 intervention within the same class
- KQ 3 same intervention with different (lower) dose (or anticoagulation goal), (less intensive) regimen, or (shorter) duration
- KQ 4 single modality intervention
- KQ 5 Same as KQ 1 and KQ 2, plus placebo and no thromboprophylaxis study arms
- KQ 6 same intervention started at different (later) time relative to surgery

Outcomes of Interest

For all KQs, except KQ 5 (the network meta-analysis), we evaluated the outcomes in the following list. We did not use strict *a priori* definitions of the outcomes, but included all reported outcomes as defined by study researchers. When necessary, we used our best judgment to categorize outcomes when studies failed to clearly define their reported outcomes (e.g., whether reported DVTs were total or symptomatic, whether reported bleeding was major).

- VTE (combined PE and DVT)
    - Total VTE (symptomatic and asymptomatic)
    - Symptomatic VTE
- PE
    - Total PE (fatal and nonfatal; symptomatic and asymptomatic)
    - Fatal PE

    - Symptomatic PE
- DVT
    - Total DVT (symptomatic and asymptomatic; proximal and distal)
    - Symptomatic DVT
    - Proximal DVT
- Postthrombotic syndrome (PTS)
- Pulmonary hypertension (due to PE)
- Adherence (compliance) with treatment
- Adverse events due to intervention(s)
    - Major bleeding, including:
        - Fatal bleeding
        - Bleeding leading to transfusion
        - Major bleeding leading to reoperation
        - Major bleeding leading to readmission
        - Surgical site / joint bleeding
        - Bleeding leading to infection
        - As defined by authors
    - Surgical site/wound-related infections
    - Surgical site/wound complications (other than bleeding, infection)
    - Heparin-induced thrombocytopenia
    - Adverse events due to mechanical devices (as reported by authors)
    - Adverse events due to IVC filter (as reported by authors)
    - Other clinically significant adverse events reported by studies

For KQ 5 (the network meta-analysis), we evaluated only *total DVT* and *major bleeding*. We included confirmed and unconfirmed VTE, but downgraded the risk of bias for those studies that analyzed unconfirmed VTE. If both confirmed and unconfirmed VTE were reported, we extracted only the confirmed VTE data.

Eligible Study Designs

For all KQs, we included randomized controlled trials (RCT) of any sample size. For KQs other than the network meta-analysis (KQ 5), we also included prospective or retrospective nonrandomized comparative studies (NRCS) with at least 750 patients per surgery type, per study. This was consistent with the 2012 report. In contrast to the 2012 VTE report, we also required at least 50 patients in each included study arm (or intervention).

We included published, peer-reviewed articles, conference abstracts and presentations, and studies reported only in the ClinicalTrials.gov Web site. Non-English language publications were extracted by researchers fluent or facile in the published languages. Unavailable publications were included and extracted only from their English language abstract.

Timing

We included studies with any duration of followup. For VTE outcomes, we extracted results at all reported timepoints, but for meta-analyses we preferentially analyzed timepoints closest to 30 days postoperative (as being the most commonly reported timepoint).

Setting

Studies performed in hospital (with or without continuation of intervention or followup after discharge)

Study Selection

We assessed titles and abstracts of citations identified from literature searches for inclusion, using the above eligibility criteria. Abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the eligibility criteria. Both abstract and full-text screening was conducted in duplicate with conflicts resolved by reconciliation among the whole research team. All rejected full-text articles were confirmed by the project lead.

Studies included in the 2012 VTE report were reassessed for inclusion based on the summarized data available in the 2012 VTE report. In general, we did not confirm eligibility criteria for these studies from the full-text articles.

Data Extraction

Each study was extracted by one methodologist and confirmed by at least one other experienced methodologist. Disagreements were resolved by open, free-flowing discussion among the team to achieve consensus. Data extraction was conducted into customized forms in the Systematic Review Data Repository (SRDR) online system designed to capture all elements relevant to the KQs (http://srdr.ahrq.gov); the completed extraction forms are available for public review at this site. These included population characteristics, including description of patients' surgery, descriptions of the interventions analyzed, descriptions of relevant outcomes, sample sizes, study design features, funding sources, results (including adverse events), and risk of bias assessment. The forms were tested on several studies and revised as necessary.

New studies added to the 2012 VTE report were extracted from the full-text articles and any available supplemental material. With few exceptions, eligible studies from the 2012 VTE report extracted and entered into SRDR based only on the available data presented in the 2012 VTE report.

Risk of Bias Assessment

We based the methodological quality of each study on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[16] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used selected questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up.[17] The methodological quality of the eligible studies from the 2012 VTE report was based solely on what was reported in that report's methodological quality tables. Risk of bias questions included in the current review that were not assessed in the 2012 VTE report were marked as "NR" (not reported).

Data Synthesis

Pairwise Meta-Analysis

For KQs 1 through 4 and 6, we conducted restricted maximum likelihood random effects model meta-analyses of four or more comparative studies that were sufficiently similar in population, interventions, and outcomes. Odds ratios (ORs) were chosen as the metric to analyze categorical outcomes. In the analysis of rare outcomes (<1%), we used Peto's OR.[18-20] Studies with no events in both trial arms were excluded as they do not contribute to the estimate of the summary effect. In the analysis by class (KQ 1), for trials containing arms with different doses of the same intervention, we included the arm with the dose that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. Pairwise meta-analyses were conducted in R using the *metafor* package. Results are presented in terms of summary ORs and the corresponding 95 percent confidence interval (CI).

Network Meta-Analysis

To address KQ 5, we conducted network meta-analyses under a Bayesian framework. The specific model is described by Dias et al.[21] Network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct comparisons (where interventions are compared head-to-head) and indirect comparisons (where interventions are compared through other reference interventions). Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that there is consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is similar across trials, and thus, patients are similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons (where the direct and indirect comparisons contradict each other).

For binary outcomes (e.g., total DVT and major bleeding), the network meta-analysis model corresponds to a generalized linear mixed model with a logit link. We included random effects on the treatment parameters, which allowed each study to have a different but related treatment effect estimate versus a reference treatment. The amount of between-study variance (heterogeneity) was assumed to be constant across all treatment comparisons. We used noninformative prior distributions for the model parameters. The models initially discarded a set of 50,000 iterations as "burn-in," and the inferences were based on additional 50,000 iterations ("runs") using 4 chains. Convergence of the chains was assessed by the Gelman-Rubin statistic and visual inspection of trace plots. Due to the sparseness of data in some networks, we also conducted analyses with an informative log-normal prior for the heterogeneity parameter.[22] The results of these analyses lead to similar conclusions as the base analysis, and are presented in Appendix G of the full report.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach.[23] This approach evaluates each treatment comparison in terms of its direct and indirect evidence estimates. Discrepancies between these estimates indicate inconsistency. Since we did not find any evidence of inconsistency, only results from the (consistency) network meta-analysis are presented. However, the inability of the models to detect inconsistency in our

evidence base with sparse data may be due to the lack of power rather than suggestive of consistent networks.

We conducted a total of 12 network meta-analyses to compare all treatment alternatives across studies. For each of three surgeries (THR, TKR, and HFx surgery) and for the two outcomes (total DVT and major bleeding) we conducted two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., LMWH, antiplatelet drugs) and 2) comparisons of individual interventions. For trials containing arms with different doses of the same intervention, we included the arm with the dose that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. For all network meta-analyses (in contrast to KQ 1-4 and 6), we included placebo/no treatment as an intervention (or class) to strengthen the network of evidence. Placebo-controlled trials were included in the network if they included active interventions that were otherwise in the network. We omitted placebo-controlled trials that would be a spur in the network (if, across trials, the intervention was compared only to placebo, not to any active intervention). Network meta-analyses were conducted in R using the *gemtc* package. Results are presented in terms of summary ORs and the corresponding 95 percent credible interval (CrI).

Summarizing Findings Across Studies

For each comparison of interventions, we determined a conclusion (or summary of findings across studies) for each outcome with sufficient evidence (i.e., not insufficient evidence, see *Grading the Strength of Evidence*).

We concluded the evidence "favors" one intervention (over the other) when

- there was a statistically significant difference by meta-analysis,
- when the preponderance of studies found a statistically significant difference in the same direction (when no meta-analysis was conducted), or
- meta-analysis found a statistically nonsignificant effect size that was either greater than 1.20 or less than 0.80.
    - However, if the 95 percent confidence interval was highly imprecise (beyond *both* 0.50 and 2.00), the conclusion was "unclear" regardless of the magnitude of the point estimate.
    - If a conclusion was based on a statistically nonsignificant effect size, the strength of evidence (see below) was low (it could not be moderate or high).

We concluded that interventions had similar effects (noted in tables as favoring "either") when summary effect sizes (by meta-analysis) or the preponderance of studies' effect sizes (when not meta-analyzed) were between 0.80 and 1.20, were not statistically significant, and were not highly imprecise or inconsistent (across studies).

When studies were sparse, effect size estimates were highly imprecise (95% confidence intervals beyond *both* 0.50 and 2.00, usually due to sparse events), or studies were highly inconsistent (e.g., with point estimates ranging from 0.14 to 3.03), we deemed the findings to be "unclear" (with an insufficient strength of evidence).

Subgroup Analyses and Metaregression

All studies were evaluated for within-study subgroup (or predictor) analyses. As feasible, studies were also categorized based on whether, as a whole, they evaluated particular populations of interest, such as studies that included at least 90 percent of a subgroup of interest, including

sex, race/ethnicity, older age group, body weight category, tobacco use, chronic disease, varicosities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, primary versus revision surgery, use of cemented fixation, tourniquet use, tranexamic acid use, anesthesia type, etc. We also investigated potential differences between studies based on industry funding. We aimed to conduct random effects model metaregressions for many variables but data were too sparse to allow meaningful analyses for most.

Grading the Strength of Evidence

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the SoE.[20] We assessed the SoE for each health outcome, as determined with input from the panel of technical experts: total VTE, symptomatic VTE, PE, DVT, and adverse events. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Throughout the report, all estimates with 95 percent CI or CrI beyond 0.5 and 2.0 were considered to be highly imprecise. Based on these assessments, we assigned a SoE rating as being either high, moderate, low, or there being insufficient evidence to estimate an effect. Conclusions based on statistically nonsignificant findings could have at best a low SoE. Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one or two studies were deemed to have insufficient evidence to allow for a conclusion (with the exception that particularly large, generalizable single studies could provide at least low SoE). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Strength of Evidence" table detailing our reasoning for arriving at the overall SoE rating.[24]

Peer Review

A draft version of this report was reviewed (from July 27 to August 23, 2016) by invited and public reviewers, including representatives from orthopedic societies, industry, our TEP, and the general public. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Summary of Studies

The literature searches yielded 1738 citations. We rescreened 118 studies that had been included in the 2012 VTE report and 107 references found in relevant existing systematic reviews. In total, 455 articles were screened in full text, of which 313 were excluded for the reasons listed in Figure 2 and Appendix B of the full report. The 142 studies included 127 RCTs and 15 NRCSs; they provided 85 studies of THR, 60 of TKR, and 12 of HFx surgery. The

publication status and sources of the studies are listed in Figure 2 of the full report. The grey literature searches added two studies, both unpublished studies with results in ClinicalTrials.gov.

Studies evaluated the following thromboprophylaxis classes (and combinations thereof): antiplatelet drugs, DTI, FEI, FXaI, FXIi, LMWH, mechanical devices, UFH, and VKA. The studies evaluated the following specific interventions (and combinations thereof): aspirin (antiplatelet drug); dabigatran and desirudin (DTIs); TB402 (FEI); apixaban, darexaban, edoxaban, eribaxaban, fondaparinux, rivaroxaban, and TAK422 (FXaIs); factor XI antisense oligonucleotide (FXIASO; FXIi); dalteparin, enoxaparin, semuloparin, and tinzaparin (LMWHs); flexion devices, graduated compression stockings (GCS), intermittent pneumatic compression (IPC), and venous foot pumps (VFP) (mechanical devices); UFH; and warfarin (VKA).

We chose the principal outcomes for this review (the various VTE outcomes, major bleeding, and serious adverse events) based on an *a priori* determination of their importance in regards to thromboprophylaxis choice decisionmaking and the high likelihood that these outcomes would be available to researches of almost all RCTs. However, only total DVT was reported by more than 80 percent of the studies (82%), an arbitrary threshold we chose to suggest high risk of reporting bias. In descending order, the remaining principal outcomes were proximal DVT (66% of studies reported), total PE (52%), major bleeding (52%), fatal PE (48%), symptomatic DVT (40%), symptomatic VTE (18%), symptomatic PE (17%), total VTE (15%), and study-defined serious adverse events (11%).

Of note, almost all studies that reported serious adverse events did not define the outcome. Presumably, it included major bleeding, but this is not clear. Two studies described them as treatment-related events that lead to death, are life-threatening, require or prolong hospitalization, cause disability or incapacity, jeopardize the subject, or require an intervention. One study referred to "standard regulatory definitions", but did not further define.

Randomized Controlled Trials

Among the RCTs, 61 (50%) reported industry funding, 4 (3%) used materials supplied by industry, 18 (15%) explicitly reported no industry support, and 40 (33%) did not provide funding information.

In general, for the RCTs the risk of bias was low regarding randomization, allocation concealment, group similarity at baseline, and methods used for outcome assessment. Reporting, compliance with interventions, timing of outcome assessment, and definition of adverse effects were explicitly reported in fewer than half of the RCTs. Fifty-two RCTs had a high risk of bias regarding blinding of patients (in addition, 16 had unclear risk of bias, 1 not reported from the original report[a]), 51 for blinding of healthcare providers (25 unclear, 1 not reported from the original report), and 20 for blinding of outcome assessors (29 unclear). Twenty-eight RCTs had a high risk of bias in compliance of intention-to-treat principle in data analysis (8 unclear). Attrition bias was rated high in 22 RCTs (10 unclear).

Nonrandomized Comparative Studies

Overall, we included 15 NRCSs. Five NRCSs evaluated only THR, six only TKR, three had separate analyses of THR and TKR, and one evaluated HFx surgery. Two reported industry

[a] The current review assessed risk of bias domains not consistently addressed by the 2012 VTE report. We did not assess these studies for these risk of bias domains, but instead marked them as "not reported".

funding, and the other 12 NRCSs explicitly reported no industry support. In general, the risk of bias was low for incomplete results reporting (2 unclear) and timing of outcome assessments (3 unclear). One NRCS had high risk of bias for adverse event reporting and one was unclear. Similarly, one NRCS had high risk of bias for compliance with interventions and a second was unclear. One NRCS had high risk of bias for patient selection, and a second was unclear. Seven NRCSs had high risk of bias for group similarity at baseline (4 unclear); five for assessment of outcomes (4 unclear). Seven NRCSs had high risk of bias for blinding of outcome assessors, and another five were unclear. Eight had high risk of bias for selective outcome reporting.

Correlation of DVT and PE Across Trials

To help put the VTE outcomes into context, we performed simple correlation analyses of rates of DVT (proximal, symptomatic, and total) and of PE (fatal, symptomatic, and total) across studies and interventions, including placebo. Analyses were run excluding studies arms with no DVT or PE events; more than half the studies that reported PE outcomes had no PE events. We also excluded studies with atypically high rates of PE (i.e., outlier studies that typically represented single events in small studies). Across studies, rates of total PE (the most commonly reported PE outcome) were correlated with symptomatic DVT ($r=0.57$), but not distal or total DVT ($|r|\leq 0.10$). Rates of symptomatic PE were correlated with rates of proximal DVT ($r=0.33$) but not symptomatic DVT ($r=0.19$). Fewer than five studies reported (non-zero) fatal PE events or both symptomatic PE and total DVT, so correlations were not assessed for associated pairs of outcomes. In summary, the rates of the most commonly reported PE and DVT outcomes (total PE and total DVT) are not correlated within these studies; however, rates of symptomatic DVT are correlated with rates of total PE across studies.

Key Question 1: Comparison of Thromboprophylaxis Intervention Classes

Note that the results of comparisons with sufficient evidence are summarized here; other comparisons were deemed to have insufficient evidence.

Total Hip Replacement

Key Points

- There were 46 RCTs and 5 NRCSs that compared classes of interventions in patients undergoing THR.
- Pairwise comparisons between classes had sufficient data for only six pairs of classes.
  - **LMWH vs. DTI**: Across outcomes there is a tradeoff between the two drug classes. Moderate SoE favors DTI to prevent total DVT and, separately, proximal DVT, but low SoE favors LMWH to avoid major bleeding.
  - **LMWH vs. FXaI**: Across outcomes, the evidence is inconsistent. The studies found that FXaI better lowers the risk of total VTE (low SoE), total DVT (moderate SoE), and proximal DVT (moderate SoE), but LMWH better lowers the risk of symptomatic VTE (low SoE) and symptomatic DVT (low SoE). There was high SoE that LMWH is better to prevent major bleeding, but both classes were similar in rates

of study-defined serious adverse events (moderate SoE). The inconsistencies in these finding suggest important reporting bias.
    - **LMWH vs. UFH**: Overall, favors LMWH, with lower risk of total PE (high SoE), proximal DVT (moderate SoE), and major bleeding (moderate SoE); risk of total DVT was similar between drug classes (moderate SoE).
    - **LMWH vs. VKA**: Overall unclear. There is insufficient evidence regarding the relative benefit of either drug class to lower the risk of any VTE outcome, but VKA results in lower risk of major bleeding (high SoE).
    - **LMWH vs. aspirin**: Based primarily on a very large propensity-score-adjusted NRCS, LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding (all low SoE).
    - **Mechanical devices vs. VKA**: Overall, unclear. VKA results in lower risk of proximal DVT (high SoE), but insufficient evidence all favors mechanical devices to lower the risk of total DVT, and adverse events data have not been reported.
    - For all other class comparisons and outcomes there was insufficient evidence.
    - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis by chronic kidney disease category was inconclusive regarding differential risks of bleeding with LMWH and DTI.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results for THR Studies

Pairwise comparisons between classes had sufficient data for at least one outcome for six pairs of classes (Table A). For the comparison of LMWH versus DTI, among four RCTs, three favored DTI to prevent total DVT and to prevent proximal DVT. Meta-analysis of the four trials found a nonsignificant difference between drug classes regarding major bleeding favoring LMWH.

LMWH versus FXaI: For the comparison of LMWH versus FXaI, among 13 RCTs there is high risk of reporting bias. Most meta-analyses of VTE outcomes significantly favored FXaI (total VTE [6 RCTs, low SoE], total DVT [10 RCTs, moderate SoE], and proximal DVT [10 RCTs, moderate SoE]). The meta-analyses of symptomatic VTE (7 RCTs, low SoE) and symptomatic DVT (9 RCTs, low SoE) found no significant differences between LMWH and FXaI, but favored LMWH; however, these RCTs mostly did not report other VTE outcomes. Major bleeding was significantly less likely with LMWH (10 RCTs, high SoE), but there was no significant difference in study-defined serious adverse events (5 RCTs, moderate SoE). Given the inconsistent findings across VTE outcomes, the relative benefit of either drug class is unclear.

LMWH versus mechanical devices: Among 3 RCTs of LMWH versus mechanical devices, none found significant differences for multiple VTE outcomes (total VTE, total PE, symptomatic PE, fatal PE, total DVT, proximal DVT). A NRCS found no difference in total PE. A single RCT reported significantly more frequent major bleeding with LMWH. Overall, the evidence was deemed to be insufficient to make conclusions about relative effect or harms between the two intervention classes.

LMWH versus UFH: From 10 RCTs, meta-analyses of LMWH versus UFH significantly favored LMWH to prevent total PE (8 RCTs, high SoE) and proximal DVT (6 RCTs, moderate SoE) and to avoid major bleeding (6 RCTs, moderate SoE), but showed no statistically significant difference in total DVT (10 RCTs, moderate SoE). Overall, the evidence favors LMWH.

LMWH versus VKA: Meta-analysis of the 4 RCTs of LMWH versus VKA found significantly lower rates of major bleeding with VKA (high SoE); however, the evidence regarding VTE is insufficient.

LMWH versus antiplatelet drug (aspirin): One very large NRCS (N=108,584) and another smaller NRCS (N=1533) compared LMWH versus antiplatelet drug (aspirin). The evidence suggests both drug classes have similar effects and harms. In both adjusted and propensity-score matched analyses, the very large NRCS found no differences in rates of total PE, symptomatic DVT, and major bleeding (all low SoE).

Mechanical devices versus VKA: Three RCTs evaluated mechanical devices versus VKA, overall yielding unclear findings regarding relative benefits and harms. The studies favored VKA to prevent proximal DVTs (high SoE), but insufficient evidence for total DVT favored mechanical devices, and there was no evidence regarding adverse events.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drug (aspirin) versus VKA (2 RCTs, one NRCS), LMWH versus antiplatelet drug (2 NRCSs), antiplatelet drug versus mechanical device (1 NRCS), mechanical device versus UFH (1 RCT), DTI versus FXaI (1 RCT), DTI versus UFH (2 RCTs), and FEI versus FXaI (1 RCT).

Table A. Total hip replacement, intervention class versus class: Summary of "sufficient" evidence

Comparison	Outcome*	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates†	Conclusions	SoE Grade
LMWH vs. DTI	DVT, total	RCT: 3 (4600)	Range 1.14 to 1.52†	Favors DTI	Moderate
	DVT, proximal	RCT: 3 (4600)	Range 1.35 to 1.89†	Favors DTI	Moderate
	Bleeding, major	RCT: 4 (6900)	0.79 (0.55, 1.14)	Favors LMWH	Low
	VTE vs. AE‡ (reported)	*RCT: 4 (6900)*		*Tradeoff: Favors DTI to prevent DVT. Favors LMWH to minimize major bleeding.*	
LMWH vs. FXaI	VTE, total	RCT: 6 (5801)	2.18 (1.52, 3.13)	Favors FXaI	Low
	VTE, symptomatic	RCT: 7 (6157)	0.72 (0.40, 1.30)	Favors LMWH	Low
	DVT, total	RCT: 10 (9346) NRCS: 1 (1056)	1.71 (1.22, 2.39)	Favors FXaI	Moderate
	DVT, symptomatic	RCT: 9 (11,954)	0.76 (0.37, 1.57)	Favors LMWH	Low
	DVT, proximal	RCT: 10 (9622)	2.40 (1.23, 4.69)	Favors FXaI	Moderate
	Bleeding, major	RCT: 10 (12,457)	0.74 (0.54, 0.99)	Favors LMWH	High
	Serious adverse events (study-defined)	RCT: 5 (6727)	0.95 (0.78, 1.17)	Either	Moderate
	VTE vs. AE‡ (reported)	*RCT: 13 (13,173)*		*Unclear: Inconsistent findings across VTE outcomes, but favors LMWH to minimize major bleeding.*	
LMWH vs. UFH	PE, total	RCT: 8 (1878)	0.29 (0.13, 0.63)	Favors LMWH	High
	DVT, total	RCT: 10 (2219)	0.84 (0.60, 1.18)	Either	Moderate
	DVT, proximal	RCT: 6 (1506)	0.59 (0.38, 0.93)	Favors LMWH	Moderate
	Bleeding, major	RCT: 6 (1960)	0.46 (0.23, 0.92)	Favors LMWH	Moderate
	VTE vs. AE‡ (reported)	*RCT: 10 (2387)*		*Favors LMWH: Lower risk VTE outcomes and major bleeding.*	
LMWH vs. VKA	Bleeding, major	RCT: 4 (5332)	1.96 (1.14, 3.38)	Favors VKA	High
LMWH vs. aspirin	PE, total	NRCS: 2 (110,117)	0.94 (0.75, 1.17)	Either	Low
	DVT, symptomatic	NRCS: 1 (108,584)	0.84 (0.70, 1.03)	Either	Low
	Bleeding, major	NRCS: 1 (108,584)	0.95 (0.77, 1.17)	Either	Low
	VTE vs. AE‡ (reported)	*NRCS: 2 (110,117)*		*Either: Similar VTE outcomes and major bleeding with LMWH and aspirin.*	
Mechanical Devices vs. VKA	DVT, proximal	RCT: 3 (434)	Range 2.39 to 4.69†	Favors VKA	High

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse events, CI = confidence interval, DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, NRCS = nonrandomized comparative study, OR = odds ratio, PE = pulmonary embolism, RCT = randomized controlled trials, UFH = unfractionated heparin, VKA = vitamin K inhibitor.

* Evaluated outcomes included total VTE, symptomatic VTE, total PE, fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† When no summary estimate was calculated by meta-analysis, the range of effect sizes (without confidence intervals) across studies is provided here.

‡ Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

Subgroup Analysis in THR Studies

One RCT reported results for serious bleeding by level of chronic kidney disease in a comparison of LMWH and DTI. Event rates were low for all participants (2% in both the desirudin and the enoxaparin arms). They reported that for chronic kidney disease category 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.112). For chronic kidney disease category 3A (n=758), the rates were the same (0.3% in both arms). For chronic kidney disease categories 1-2 (n=700), DVT rates were lower in the enoxaparin arm (0.6% vs. 0%).

Studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithrombotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregression no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregression. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Total Knee Replacement

Key Points

- There were 29 RCTs and 6 NRCSs that compared classes of interventions in patients undergoing TKR.
- Pairwise comparisons between classes had sufficient data for meta-analyses for only two pairs of classes.
  - **LMWH vs. FXaI**: Overall, the evidence is unclear. FXaI results in a lower risk of total VTE (low SoE), total DVT (low SoE), and proximal DVT (moderate SoE), but similar risks for total VTE (moderate SoE) and symptomatic DVT (low SoE); risk of major bleeding is lower with LMWH (low SoE) but risk of study-defined serious adverse events is lower with FXaI (low SoE).
  - **LMWH vs. VKA**: There is a tradeoff in risks between the two drug classes, such that LMWH better lowers risk of total DVT (high SoE) and proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE).
  - For all other class comparisons and outcomes there was insufficient direct comparative evidence.
  - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results for TKR Studies

Pairwise comparisons between classes had sufficient data for meta-analysis for only two pairs of classes (Table B).

LMWH versus FXaI: For the comparison of LMWH versus FXaI, across 10 RCTs, meta-analysis significantly favored FXaI to prevent total DVT (7 RCTs) and proximal DVT (6 RCTs). While not statistically significant, the evidence favored FXaI to reduce the risk of total VTE (4 RCTs) with lower rates of study-defined serious adverse events (4 RCTs). Major bleeding occurred (nonsignificantly) less frequently with LMWH (7 RCTs). Rates of symptomatic DVT were the same with both drug classes (8 RCTs).

LMWH versus VKA: Among 4 RCTs that compared LMWH versus VKA, LMWH treatment resulted in less frequent total DVT (nonsignificantly) in 3 RCTs and proximal DVT across 4 RCTs (also not statistically significant); 4 RCTs found (nonsignificantly) lower risk of major bleeding with VKA.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drug versus FXaI (1 RCT), antiplatelet drug versus mechanical devices (1 RCT, 1 NRCS), antiplatelet drug (aspirin) versus VKA (1 RCT), DTI versus FXaI (1 RCT), LMWH versus antiplatelet drug (1 RCT), LMWH versus FXIi (1 RCT), LMWH versus mechanical devices (1 RCT and 1 NRCS), LMWH versus UFH (2 RCTs), and VKA versus mechanical devices (1 NRCS). Five RCTs evaluated LMWH vs. DTI but had highly inconsistent findings related to symptomatic DVT (3 RCTs) and rare episodes of major bleeding resulting in a highly imprecise effect estimate (5 RCTs).

Table B. Total knee replacement, intervention class versus class: Summary of "sufficient" evidence

Comparison	Outcome*	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates†	Conclusions	SoE Grade
LMWH vs. FXaI	VTE, total	RCT: 4 (1260)	1.33 (0.89, 1.99)	Favors FXaI	Low
	DVT, total	RCT: 7 (3805)	2.09 (1.70, 2.58)	Favors FXaI	Low
	DVT, symptomatic	RCT: 8 (5715)	0.99 (0.51, 1.91)	Either	Low
	DVT, proximal	RCT: 6 (4402)	1.84 (1.07, 3.16)	Favors FXaI	Moderate
	Bleeding, major	RCT: 7 (5926)	0.74 (0.42, 1.30)	Favors LMWH	Low
	Serious AE (study-defined)	RCT: 4 (1803)	1.51 (0.80, 2.85)	Favors FXaI	Low
	VTE vs. AE‡ (reported)	*RCT: 10 (6350)*		*Unclear: Favors FXaI to prevent VTE outcomes, but inconsistent regarding major bleeding and serious adverse events.*	
LMWH vs. VKA	DVT, total	RCT: 3 (1742)	Range 0.42 to 0.67†	Favors LMWH	High
	DVT, proximal	RCT: 4 (1772)	0.51 (0.21, 1.28)	Favors LMWH	Low
	Bleeding, major	RCT: 4 (1960)	Range 1.16 to 3.13†	Favors VKA	Low
	VTE vs. AE‡ (reported)	*RCT: 4 (1960)*		*Tradeoff: Favors LMWH to prevent DVT. Favors VKA to minimize major bleeding.*	

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse events, CI = confidence interval, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, OR = odds ratio, RCT = randomized controlled trials, VKA = vitamin K inhibitor.

* Evaluated outcomes included total VTE, symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† When no summary estimate was calculated by meta-analysis, the range of effect sizes (without confidence intervals) across studies is provided here.

‡ Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

Subgroup Analysis in TKR Studies

One RCT compared subgroups of patients who received unilateral or bilateral TKR surgery in a comparison of antiplatelet drug (aspirin) versus mechanical device; the trial was conducted in the 1980s and included an unrestricted sample of adult patients undergoing TKR. They found that in the unilateral surgery group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral surgery group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20). Whether the treatment effect differed between unilateral and bilateral surgery subgroups was not analyzed.

Studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregression no significant difference (P=0.21) was found between the six industry-funded

studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregression. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Hip Fracture Surgery

Key Points

- There were 6 RCTs that compared classes of interventions in patients undergoing HFx surgery.
- No drug class comparison had sufficient data for meta-analysis. One comparison had sufficient data for an effect conclusion.
  - **LMWH vs. FXaI**: Overall, the evidence is unclear. There is moderate SoE that LMWH results in a lower risk of total DVT. There is insufficient evidence for all other outcomes, including adverse events.
  - For all other class comparisons and outcomes there was insufficient direct comparative evidence.

Summary Results for HFx Studies

Only 6 RCTs of thromboprophylaxis have been conducted comparing intervention classes in patients undergoing HFx surgery. Pairwise comparisons between classes had sufficient data only for the comparison of LMWH versus FXaI (Table C). The 3 RCTs that compared LMWH versus FXaI found lower risk of total DVT with LMWH, but there was insufficient evidence regarding other outcomes. Other interventions classes compared included antiplatelet drug (aspirin) versus mechanical devices (1 RCT), antiplatelet drug (aspirin) versus VKA (1 RCT), and LMWH versus UFH (1 RCT); there was insufficient evidence regarding these comparisons.

Table C. Hip fracture surgery, intervention class versus class: Summary of "sufficient evidence"

Comparison	Outcome*	Design: No. Studies (N)	Estimates	Conclusions	SoE Grade
LMWH vs. FXaI	DVT, total	RCT: 3 (1816)	0.55,† 2.71, 3.81	Favors LMWH	Moderate

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin; RCT = randomized controlled trials.

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† This low estimate (0.55) was highly imprecise and nonsignificant (95% confidence interval 0.05, 5.58). The other two estimates were precise and statistically significant. The imprecision of the low estimate makes it, in fact, consistent with the two other significant estimates.

Key Question 2: Comparison of Within-Class Thromboprophylaxis Interventions

Relatively few RCTs of thromboprophylaxis compared specific interventions within any given class (3 for THR, 2 for TKR, and 2 for HFx surgery). No comparison was evaluated by more than two studies.

In patients undergoing THR or TKR (in separate analyses), one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). In patients with HFx surgery, one RCT each compared enoxaparin versus dalteparin (LMWHs) and enoxaparin versus semuloparin (LMWHs). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations of Thromboprophylaxis Interventions

Key Points

- There were 22 RCTs and 2 NRCSs that compared different intervention doses or durations in patients undergoing THR, 18 RCTs and 1 NRCS in patients undergoing TKR, and 2 RCTs in patients undergoing HFx surgery.
- Only a small number of drug (or class) dose or duration comparisons had sufficient data.
  - **THR**
    - **FXaI low vs. high dose**: Overall, the evidence is unclear.. There is low SoE that higher dose FXaI (darexaban 30 to 60 mg, edoxaban 30 mg) has a lower risk of total VTE than lower dose FXaI (darexaban 10 to 15 mg, edoxaban 15 mg), but there is insufficient evidence for other outcomes, including adverse events.
    - **LMWH low vs. high dose**: There is evidence of a tradeoff between low and high dose LMWH. Higher dose LMWH (e.g., enoxaparin 40 mg) results in a lower risk of total DVT than lower dose LMWH (e.g., enoxaparin 20 to 30 mg) (low SoE), but both high and low dose LMWH result in similar risk of proximal DVT. Lower dose LMWH has a lower risk of major bleeding than higher dose LMWH (moderate SoE).
    - **LMWH short vs. long duration**: The evidence supports longer duration LMWH. Longer duration LMWH (>2 weeks) results in lower risk of total PE (low SoE), total DVT (high SoE), and proximal DVT (moderate SoE) than shorter duration LMWH (up to 10 days or to hospital discharge); bleeding events were rare in the LMWH studies yielding insufficient evidence regarding relative difference in risk.
  - **TKR**
    - **DTI low vs. high dose**: There is evidence of a tradeoff between low and high dose DTI. Higher dose DTI (dabigatran 220 to 225 mg) has a lower risk of total DVT (high SoE) and proximal DVT (moderate SoE) than lower dose (dabigatran 150 mg), but lower dose DTI has less risk of major bleeding (low SoE)

- **FXaI low vs. high dose**: Overall, the evidence is unclear. Higher dose FXaI (e.g., edoxaban 60 mg, darexaban 30 mg) results in a lower risk of total VTE (moderate SoE), symptomatic DVT (low SoE), and proximal DVT (low SoE) than lower dose FXaI (e.g., edoxaban 5 mg, darexaban 15 mg); however, there was insufficient evidence for adverse events.

- **HFx surgery**
  - Data were insufficient to summarize the evidence for different dose or duration of interventions for HFx surgery

Summary Results for Key Question 3

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level analyses; comparisons of individual thromboprophylaxis interventions within classes were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

Total Hip Replacement

For three pairwise comparisons of dose or treatment duration, there was sufficient data (Table D). Among four RCTs comparing FXaI low versus high doses, meta-analysis yielded a nonsignificant effect favoring high dose FXaI to prevent total VTE. Data were insufficient for other outcomes.

Five RCTs compared LMWH low versus high doses. Meta-analysis of the five RCTs found a nonsignificant effect on total DVT favoring higher dose LMWH. Meta-analysis found no difference in effect on proximal DVTs (4 RCTs). By meta-analysis, there was significantly less risk of major bleeding with lower dose LMWH (4 RCTs).

Among six RCTs of LMWH short versus long duration treatment, long duration LMWH resulted in fewer total PE (5 RCTs), but the summary OR was not statistically significant. Long duration LMWH resulted in statistically significantly lower risk of total DVT (6 RCTs) and proximal DVTs (5 RCTs). Data were insufficient for adverse events.

Table D. Total hip replacement, comparison of different doses or treatment durations: Summary of "sufficient" evidence

Comparison	Outcome*	Design: No. Studies (N)	Summary OR (95% CI	Conclusions	SoE Grade
FXaI low vs. high dose	VTE, total	RCT: 4 (981)	1.55 (0.78, 3.06)	Favors high dose	Low
LMWH low vs. high dose	DVT, total	RCT: 5 (1441)	1.33 (0.56, 3.18)	Favors high dose	Low
	DVT, proximal	RCT: 4 (1047)	1.04 (0.55, 1.98)	Either	Low
	Major bleeding	RCT: 4 (1498)	0.42 (0.21, 0.86)	Favors low dose	Moderate
	VTE vs. AE† (reported)	*RCT: 5 (1580)*		*Tradeoff: Favors higher dose to prevent total DVT. Favors lower dose to minimize major bleeding.*	
LMWH short vs. long duration	PE, total	RCT: 5 (1128)	2.73 (0.97, 7.64)	Favors long duration	Low
	DVT, total	RCT: 6 (1463)	2.87 (2.08, 3.96)	Favors long duration	High
	DVT, proximal	RCT: 5 (1300)	2.94 (1.62, 5.35)	Favors long duration	Moderate

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse events, CI = confidence interval, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, OR = odds ratio, PE = pulmonary embolism, RCT = randomized controlled trials.

* Evaluated outcomes included total VTE, symptomatic VTE, total PE, fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

Total Knee Replacement

For only two pairwise comparisons of dose or treatment duration were there sufficient data (Table E). Among five RCTs of low versus high dose DTI, studies favored higher dose DTI (e.g., dabigatran 220 mg/day) over lower dose DTI (e.g., dabigatran 150 mg/day) to prevent total DVT (3 RCTs) and proximal DVT (4 RCTs). By meta-analysis the five RCTs nonsignificantly favored lower dose DTI to avoid major bleeding.

Among four RCTs of low versus high dose FXaI, studies favored higher dose FXaI (multiple drugs, mostly twice the lower dose) over lower dose FXaI to prevent total VTE (4 RCTs), symptomatic DVT (4 RCTs), and proximal DVT (4 RCTs). Four RCTs were highly imprecise and inconsistent regarding difference in major bleeding risk, thus providing insufficient evidence.

Table E. Total knee r eplacement, comparison of different doses or treatment durations: Summary of "sufficient" evidence

Comparison	Outcome*	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates†	Conclusions	SoE Grade
DTI low vs. high dose	DVT, total	RCT: 3 (577)	Range 1.54 to 2.08†	Favors high dose	High
	DVT, proximal	RCT: 4 (1860)	1.57 (0.83, 2.96)	Favors high dose	Moderate
	Bleeding, major	RCT: 5 (3875)	0.65 (0.34, 1.24)	Favors low dose	Low
	VTE vs. AE‡ (reported)	*RCT: 5 (3875)*		Tradeoff: Favors higher dose to prevent DVT. Favors lower dose to minimize major bleeding.	
FXaI low vs. high dose	VTE, total	RCT: 4 (779)	2.06 (1.48, 2.86)	Favors high dose	Moderate
	DVT, symptomatic	RCT: 4 (802)	Range 2.93 to 4.37†	Favors high dose	Low
	DVT, proximal	RCT: 4 (784)	2.51 (0.85, 7.42)	Favors high dose	Low

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse events, CI = confidence interval, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, OR = odds ratio, RCT = randomized controlled trials.

* Evaluated outcomes included total VTE, symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events.

† If no summary estimate was calculated by meta-analysis, the range of effect sizes (without confidence intervals) across studies is provided here.

‡ Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

Hip Fracture Surgery

One RCT each compared different duration FXaI and LMWH, providing insufficient evidence.

Key Question 4: Comparison of Single Versus Combination Thromboprophylaxis Intervention Classes

Key Points

- There were 7 RCTs and 2 NRCSs that compared single versus combined classes of intervention in patients undergoing THR, 8 RCTs and 3 NRCSs in patients undergoing TKR, and no studies in patients undergoing HFx surgery.
- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE overall or avoid adverse events.

Summary Results for Key Question 4

Relatively few studies directly compared combination versus single interventions. Most specific comparisons were made by one study only.

For THR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and antiplatelet drug, DTI, FXaI, and mechanical device; mechanical device alone versus the mechanical device and antiplatelet drug, both antiplatelet drug and UFH, and VKA; and UFH alone versus combination UFH and LMWH. In addition, one RCT compared combination antiplatelet drug and UFH versus combination antiplatelet drug, UFH, and mechanical device.

Similarly, for TKR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus combination antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and FEI or mechanical device, and UFH alone versus combination UFH and LMWH.

No studies compared single class and combination class interventions after HFx surgery.

Key Question 5: Network Meta-Analyses Across Classes of Thromboprophylaxis Interventions

For all three major orthopedic surgeries, network meta-analyses that included more than sparse connections could be constructed only for total DVT and major bleeding. Due to incomplete and selective outcome reporting by most articles, other outcomes were too sparsely populated to allow interpretable networks. Overall, network meta-analysis findings were consistent with direct, pairwise comparisons, with the caveat that they pertain only to total DVT and major bleeding.

When interpreting the findings of the network meta-analyses, it is important to recognize that the exact ranking of interventions is susceptible to change with the addition of more studies. Interventions with relatively sparse data are likely to have imprecise rankings (i.e., to have flat rank graphs with similar likelihood across a range of ranks); see rank graphs for each network. Furthermore, while the pairwise comparisons with a network yield summary estimates and confidence intervals, the rankings of interventions are not supported by evaluations of statistical significance. Conclusions on total DVT may not translate to other, clinically significant, VTE

outcomes, as suggested by the lack of correlation across studies between rates of total DVT and total PE.

Key Points

- Conclusions from all network meta-analyses are limited due to the sparseness of direct comparisons between most interventions within each network.
- Conclusions are also limited because there were sufficient data to allow network meta-analyses only for total DVT and major bleeding, not other, clinically significant, VTE outcomes or adverse events.
- Findings were consistent with direct, pairwise comparisons of interventions to lower the risk of total DVT and major bleeding.
- Within network meta-analyses, the exact ranking of interventions is susceptible to change with the addition of more studies and the ranking orders are not supported by evaluations of statistical significance.
- For patients undergoing **THR**, network meta-analysis suggests that
  - **By class**
    - Among 53 RCTs, FXaI and DTI are most likely to be most effective to prevent **total DVT;** mechanical devices, LMWH, VKA, and UFH are less effective (moderate SoE). Other intervention classes have too sparse evidence to provide sufficient conclusions.
    - Among 32 RCTs, LMWH is more likely to result in fewer **major bleeding** events than FXaI (low SoE). Other intervention classes have too sparse evidence to provide sufficient conclusions.
  - **By intervention**
    - Among 54 RCTs, dalteparin is most likely to be most effective to prevent **total DVT**, compared with enoxaparin, IPC, UFH, and, warfarin (moderate SoE). Other interventions have too sparse evidence to provide sufficient conclusions.
    - Despite 34 RCTs, comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of **major bleeding**.
- For patients undergoing **TKR**, network meta-analysis suggests that
  - **By class**
    - Among 31 RCTs, FXaI is more effective to prevent **total DVT** versus LMWH (low SoE).
    - Among 23 RCTs, LMWH is more likely to result in fewer **major bleeding** events than FXaI (low SoE).
    - Other intervention classes have too sparse evidence to provide sufficient conclusions.
  - **By intervention**
    - Among 33 RCTs for **total DVT** and 24 RCTs for **major bleeding**, data were too sparse to yield sufficient conclusions.
- For patients undergoing either **HFx surgery**, network meta-analysis suggests that comparisons between specific pairs of classes or of interventions were too sparse to yield sufficient conclusions regarding risks of **total DVT or major bleeding**.

- **By class**
  - There were 6 RCTs that compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding, but there were insufficient data to draw conclusions.
- **By class**
  - There were 8 RCTs that compared specific interventions for total DVT and 6 for major bleeding, but there were insufficient data to draw conclusions.

Total Hip Replacement

Total Deep Vein Thrombosis

Comparison of Classes by Network Meta-Analysis in THR Studies

There were 53 RCTs that evaluated interventions in at least two classes and reported total DVT after THR. Across this study set, 10 classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, LMWH plus mechanical device, mechanical device, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (11 RCTs), UFH (10 RCTs) and placebo (12 RCTs). Antiplatelet drug was directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Overall, the combination of LMWH plus mechanical device had the highest probability of being among the top three intervention classes (99%) to prevent total DVT in patients undergoing THR, followed by FXaI (64%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (86%), and VKA (80%).

However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drug, FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, compared with mechanical devices, LMWH, VKA, and UFH.

Comparison of Specific Interventions by Network Meta-Analysis in THR Studies

In the analysis by drug (or mechanical device), there were 54 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included. Across this study set, 20 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, VFP, warfarin, placebo). Of the 190 possible pairwise comparisons, 33 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with UFH (7 RCTs) and placebo (8 RCTs). Dalteparin was directly compared with UFH, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was directly compared with placebo; TB402 was directly compared with rivaroxaban only.

Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions (96%) to prevent DVT after THR, followed by apixaban (67%). The interventions likely to be among the bottom three interventions were placebo (97%) and warfarin (58%).

However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (most interventions), dalteparin is most effective to prevent total DVTs, compared with enoxaparin, IPC, UFH, and warfarin.

Major Bleeding

Comparison of Classes by Network Meta-Analysis in THR Studies

There were 32 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR. Across this study set, 9 classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, mechanical device, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (11 RCTs), UFH (6 RCTs) and placebo (6 RCTs). Antiplatelet drug was directly compared with placebo only; FEI was directly compared with FXaI only.

Overall, the mechanical devices had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by antiplatelet drug (89%) and VKA (78%). The interventions likely to be among the bottom three interventions were FEI (>99%) and UFH (88%).

However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH was more likely to result in fewer major bleeding events than FXaI.

Comparison of Specific Interventions by Network Meta-Analysis in THR Studies

In the analysis by drug (or mechanical device), there were 34 RCTs that evaluated at least two interventions and reported major bleeding after THR. Across this study set, 17 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, warfarin, placebo). Of the 136 possible pairwise comparisons, 23 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 13 other interventions; most frequently with UFH (5 RCTs) and placebo (6 RCTs). Dalteparin was directly compared with UFH, warfarin, and edoxaban only; aspirin was directly compared with placebo only; TB402 was directly compared with rivaroxaban only.

Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (63%). The interventions likely to be among the bottom three interventions were TB402 (>99%) and aspirin (86%).

However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Total Knee Replacement

Total Deep Vein Thrombosis

Comparison of Classes by Network Meta-Analysis in TKR Studies

There were 31 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR. Across this study set, 12 classes were evaluated (antiplatelet drug [aspirin], antiplatelet drug plus mechanical device, DTI, FXaI, FXaI plus mechanical devices, FXIi,

LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 66 possible pairwise comparisons, 20 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drug plus mechanical device was directly compared with antiplatelet drug and LMWH plus mechanical device; the combination of FXaI plus mechanical device was directly compared with FXaI only.

Overall, FXaI had the highest probability of being among the top three intervention classes (84%) to prevent DVT after TKR, followed closely by the combination of LMWH plus mechanical device (81%), then the combination of antiplatelet drug plus mechanical device (66%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drug (86%), and VKA (76%).

However, except for LMWH and FXaI (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. FXaI is more effective to prevent total DVTs than LMWH.

Comparison of Specific Interventions by Network Meta-Analysis in TKR Studies

In the analysis by drug (or mechanical device), there were 33 RCTs that evaluated at least two interventions and reported total DVT after TKR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included. Across this study set, 23 interventions were evaluated (apixaban, aspirin, aspirin plus IPC, aspirin plus VFP, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, enoxaparin plus VFP, flexion, fondaparinux, FXIASO, UFH, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 253 possible pairwise comparisons, 34 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin plus GCS was directly compared with enoxaparin plus IPC only; IPC and aspirin plus VFP were directly compared with aspirin only; aspirin plus IPC was directly compared with enoxaparin plus IPC only; and edoxaban plus VFP was directly compared with edoxaban only.

Overall, rivaroxaban had the highest probability (68%) of being among the top three interventions to prevent DVT after TKR, followed by flexion (65%) and the combination of enoxaparin plus VFP (63%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%) and placebo (76%).

However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Major Bleeding

Comparison of Classes by Network Meta-Analysis in TKR Studies

There were 23 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drug (aspirin) versus the combination of antiplatelet drug plus mechanical device did not connect to the network of evidence and was not included. Across this study set, 8 classes were evaluated (DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, UFH, VKA, placebo). Of the 28 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with each of six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs). The combination of FXaI plus mechanical device was directly

compared to FXaI only.

Across all comparisons, there were no statistically significant differences. Overall, VKA had the highest probability of being among the top three intervention classes (84%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did not provide major bleeding data except for the one study of FXaI plus mechanical device versus FXaI. The interventions likely to be among the bottom three interventions were FXIi (68%) and FXaI (60%).

However, except for LMWH and FXaI (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. LMWH was more likely to result in fewer major bleeding events than FXaI.

Comparison of Specific Interventions by Network Meta-Analysis in TKR Studies

In the analysis by drug (or mechanical device), there were 24 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus the combination of aspirin plus VFP did not connect to the network of evidence and was not included. Across this study set, 15 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, eribaxaban, fondaparinux, FXIASO, UFH, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 105 possible pairwise comparisons, 22 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with each of 13 other interventions; most frequently with dabigatran (5 RCTs). The combination of edoxaban plus VFP was directly compared with edoxaban only.

Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did not provide major bleeding data except for one study of the combination of edoxaban plus VFP versus edoxaban. The interventions likely to be among the bottom three interventions were darexaban (96%) and fondaparinux (65%).

However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Hip Fracture Surgery

Total Deep Vein Thrombosis

Comparison of Classes by Network Meta-Analysis in HFx Surgery Studies

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drug (aspirin) versus mechanical device did not connect to the network of evidence. Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

There were no statistically significant differences. Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions. However, data were sparse and only LMWH was directly compared to

more than two other interventions by at least two RCTs each (for two comparisons).

Comparison of Specific Interventions by Network Meta-Analysis in HFx Surgery Studies

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. One RCT of aspirin versus VFP did not connect to the network of evidence. Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, UFH, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. UFH was directly compared with dalteparin only.

Overall, UFH had the highest probability of being among the top three interventions to prevent DVT after HFx surgery (95%), followed by fondaparinux (89%) and dalteparin (70%). The other three interventions were likely to be among the bottom three interventions: placebo (92%), enoxaparin (79%), and edoxaban (79%). However, no intervention was directly compared to two other interventions by at least two RCTs.

Major Bleeding

Comparison of Classes by Network Meta-Analysis in HFx Surgery Studies

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery. Across this study set, five classes were evaluated (antiplatelet drug [aspirin], FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. Placebo was the most common comparator, being directly compared with each of the four other intervention classes.

There were no statistically significant differences. Overall, antiplatelet drug had the highest probability of being among the top two interventions (96%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (52%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (96%). However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Comparison of Specific Interventions by Network Meta-Analysis in HFx Surgery Studies

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery. Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, and placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (95%) and warfarin (94%). The interventions likely to be among the bottom three interventions were fondaparinux (82%), semuloparin (77%), and enoxaparin (67%). However, only enoxaparin and fondaparinux were directly compared by two RCTs, with similar risk of major bleeding.

Key Question 6: Comparison of Different Start Times of Thromboprophylaxis Interventions

Only two RCTs compared LMWH started at different times relative to THR surgery. No eligible studies evaluated patients with TKR or HFx surgery. There was insufficient evidence to yield conclusions.

Discussion

As reviewed in the 2012 VTE report, there is a high SoE from prior research that VTE prophylaxis after major orthopedic surgery reduces the incidence of DVTs, in comparison to no (or placebo) prophylaxis; although the rarity of postoperative PE makes difficult a definitive answer to whether thromboprophylaxis is effective to reduce PE or death.[13] Systemic (i.e., nonmechanical) interventions also in general increase the risk of postoperative bleeding, compared to no (or placebo) prophylaxis.[13] Because of the presumed strong relationship between DVTs (particularly proximal DVTs) and resultant PEs, some form of thromboprophylaxis has become standard of care after major orthopedic surgery. The question of the relative effectiveness and safety of different thromboprophylaxis interventions remained uncertain as of the 2012 VTE report.

A large volume of evidence has been garnered comparing intervention options to prevent VTE in patients undergoing THR, TKR, and HFx surgery. In total this systematic review addressing comparative effectiveness and harms of drug and mechanical interventions included 127 RCTs and 15 large NRCSs examining head-to-head comparisons. The review explicitly evaluates direct comparative information and does not examine placebo-controlled effectiveness studies (with the exception of including placebo trials in the network meta-analyses). These studies pertain to three different surgeries and include nine different classes of intervention and 21 specific interventions (plus 6 combinations of classes or interventions). Furthermore, the studies disproportionately (78%) evaluated LMWH and enoxaparin in particular (60%). Thromboprophylactic interventions that are most likely to have lower risk of major bleeding (particularly aspirin and mechanical devices, for which there is limited research funding support compared with newer pharmaceutical interventions) have been inadequately studied in direct comparison studies, severely limiting strong conclusions regarding their relative effectiveness and safety. In addition, studies implicitly used a variety of specific orthopedic surgical techniques, but generally failed to describe these sufficiently to allow cross-study comparisons based on surgical techniques (or VTE- or bleeding-risk status of patients); no study reported within-study comparisons of different patients based on these characteristics. Studies also differed in regard to the specific VTE outcomes that were reported. Most studies reported total DVT (82%), which includes asymptomatic DVTs and is thus not routinely diagnosed and may not be clinically important as pertains to PE and other clinical vascular outcomes. Between one-third and two-thirds of studies did not report the other, more clinically important, VTE outcomes (e.g., symptomatic DVT). Based on an imperfect analysis across generally relatively small studies, we found that rates of total DVT are not correlated with rates of total PE (r=0.07); although, this analysis is also hampered by the fortuitous fact that few study participants had a PE. Because PEs are relatively rare, total DVTs have become a common primary outcome for VTE prophylaxis studies in part to increase power (since total DVTs are more common than symptomatic DVTs); however, reliance on this outcome may result in biased conclusions if some

interventions are more effective at preventing asymptomatic or distal DVTs (and thus total DVTs) but not more effective at preventing clinically significant DVTs. Because of (potentially biased) incomplete reporting of all VTE outcomes, it is not possible to assess whether total DVT is an appropriate proxy for PE, death, or long-term sequelae secondary to DVTs.

The current review summarizes several advances in the literature base and interpretation since the 2012 VTE report. Newer studies led to a clearer understanding that there is a tradeoff between VTE and major bleeding with either LMWH or DTIs. There are also new studies of FXaI, but its relative effect compared to LMWH remains unclear due to inconsistencies across different VTE outcomes and adverse events. Observational studies allowed a new conclusion that LMWH and aspirin have similar effects on total PE, symptomatic DVT, and major bleeding, with low SoE. New evidence also supports tradeoffs between higher and lower dose LMWH and DTI in regards to VTE outcomes and major bleeding, and that higher dose FXaI results in lower risk of total VTE than lower dose. Compared to the 2012 VTE report, similar conclusions were reached regarding the relative benefits of LMWH over UFH, the tradeoff between VTE and major bleeding with LMWH versus VKA, and the superiority of longer duration LMWH than shorter duration.

The large majority of studies compared different intervention classes (relevant to Key Question 1), but few compared specific interventions within a class (Key Question 2); different doses, regimens, or intervention durations (Key Question 3); combinations of intervention classes (Key Question 4); or different treatment start times (Key Question 6). Therefore, many of the conclusions (answers to the Key Questions) are highly limited due to insufficient evidence. In particular, conclusions are limited to the specific intervention comparisons and outcomes for which there was sufficient evidence. In addition, for most analyses, there is substantial concern about reporting bias (see *Evidence and Analysis Limitations*).

When summarizing a body of evidence, different approaches can be taken to draw conclusions from the evidence and to determine SoE. The choice of approach can have a major impact on determining whether interventions differ in their effects, interventions have similar effects, or data are inconclusive (or insufficient) regarding relative effect. Specific users of this evidence summary may differ in the assumptions they would make (e.g., whether statistically nonsignificant effects can be said to favor one intervention over another) or in the choice of minimal differences thought to be clinically important. This summary of the evidence uses a threshold of <0.80 or >1.20 to suggest that an intervention is favored to reduce the risk of the given outcome, regardless of statistical significance, analogous to a minimal clinical important difference of approximately 20 percent. Notably, statistically nonsignificant effect sizes greater than 20 percent could yield (low SoE) conclusions of differences in effect between interventions.

Evidence Summary

Total Hip Replacement

In summary, from direct comparisons for THR the evidence suggests that

- There is a tradeoff between LMWH and DTI, such that DTI prevents more total DVTs (moderate SoE) and proximal DVTs (moderate SoE) but LMWH results in less major bleeding (low SoE)
- The evidence is inconsistent regarding LMWH and FXaI in that studies reported that FXaI better lowers risk of total VTE (low SoE), total DVT (moderate SoE), and proximal DVT (moderate SoE), but LMWH better lowers the risk of symptomatic VTE (low SoE)

and symptomatic DVT (low SoE). There is high SoE that LMWH is better to prevent major bleeding, but both classes have similar rates of study-defined serious adverse events (moderate SoE). The inconsistencies in these finding suggest important reporting bias.

- Evidence regarding LMWH vs. UFH favors LMWH with lower risk of total PE (high SoE), proximal DVT (moderate SoE), and major bleeding (moderate SoE); risk of total DVT is similar between drug classes (moderate SoE).
- The relative effect of LMWH vs. VKA is unclear. There is insufficient evidence regarding the relative benefit of either drug class to lower the risk of any VTE outcome, but VKA results in lower risk of major bleeding (high SoE).
- LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding (all low SoE, based on observational studies only).
- The relative effect of VKA vs. mechanical devices is unclear. VKA results in lower risk of proximal DVT (high SoE), but insufficient evidence all favors mechanical devices to lower the risk of total DVT, and adverse events data have not been reported.
- The relative effect of lower vs. higher dose FXaI is unclear. Higher dose FXaI has a lower risk of total VTE (low SoE), but there is insufficient evidence for other outcomes, including adverse events.
- There is a tradeoff between lower and higher dose LMWH, such that higher dose LMWH has a lower risk of total DVT (low SoE), both dose levels have similar risks of proximal DVT (moderate SoE), and lower dose LMWH has a lower risk of major bleeding (moderate SoE).
- The evidence favors longer duration LMWH (>2 weeks) over shorter duration LMWH (up to 10 days or to hospital discharge), with lower risk of total PE (low SoE), total DVT (high SoE), and proximal DVT (moderate SoE) and rare occurrences of major bleeding with any duration.

Network meta-analyses pertain only to total DVT and major bleeding; they suggest that

- FXaI and DTI may be most effective to prevent total DVT compared with mechanical devices, LMWH, VKA, and UFH (moderate SoE)
- LMWH is more likely to result in fewer major bleeding events than FXaI (low SoE)
- Dalteparin is most likely to be most effective to prevent total DVTs compared with enoxaparin, IPC, UFH, and warfarin (moderate SoE)

Most outcomes were not reported by many studies, resulting in reporting bias across the evidence base. A within-study subgroup analysis was inconclusive regarding differential risks of bleeding with LMWH and DTI by chronic kidney disease category. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Total Knee Replacement

Fewer studies of TKR (than THR) yielded fewer conclusions with sufficient evidence. In summary, from direct comparisons for TKR the evidence suggests that

- The relative effect of FXaI vs. LMWH is unclear. FXaI results in a lower risk of total VTE (low SoE), total DVT (low SoE), and proximal DVT (moderate SoE), but similar risks for symptomatic DVT (low SoE); risk of major bleeding is lower with LMWH (low SoE) but risk of study-defined serious adverse events is lower with FXaI (low SoE).

- There is a tradeoff between LMWH and VKA, such that LMWH better lowers risk of total DVT (high SoE) and proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE).
- There is a tradeoff between lower and higher dose DTI, such that higher dose DTI (dabigatran 220 to 225 mg) has a lower risk of total DVT (high SoE) and proximal DVT (moderate SoE) than lower dose (dabigatran 150 mg), but lower dose DTI has less risk of major bleeding (low SoE).
- The relative effect of lower vs. higher dose FXaI is unclear. Higher dose FXaI results in a lower risk of total VTE (moderate SoE), symptomatic DVT (low SoE), and proximal DVT (low SoE); however, there is insufficient evidence for adverse events.

From network meta-analyses,

- FXaI is more likely to be effective to prevent total DVT than LMWH (low SoE)

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug versus mechanical device between unilateral or bilateral TKR surgery. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Hip Fracture Surgery

Only 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. Most specific comparisons were addressed by only one study.

- The relative effect of LMWH and FXaI is unclear. LMWH results in lower risk of total DVT than FXaI (moderate SoE), but there is insufficient evidence for other outcomes.
- For all other comparisons and for all other Key Questions the SoE is insufficient regarding HFx surgery.

Evidence and Analysis Limitations

As noted in the evidence summary, despite the large number of trials addressing thromboprophylaxis in patients undergoing major orthopedic surgery, there is inadequate evidence to confidently compare the effectiveness and the major adverse events of the myriad treatment options. As noted, the large majority of evidence pertains to LMWH (specifically enoxaparin), limiting the ability to compare all interventions. In particular, there are sparse RCTs or NRCSs that evaluated antiplatelet drugs (e.g., aspirin), VKA (e.g., warfarin), or mechanical devices.

The network meta-analyses provided greater power to compare all intervention classes and all interventions, but the sparseness of direct (within-study) comparisons for many of the interventions meant that meaningful conclusions could be derived for only a small subset of the interventions. However, the network meta-analyses are subject to important caveats. The sparseness of direct comparisons between most interventions within each network weakened the structure and the conclusions from the network meta-analyses. The only VTE outcome with sufficient evidence to allow network meta-analysis was total DVT, which is of questionable clinical significance since it includes asymptomatic and distal DVTs which have not been demonstrated to be associated with increased risk of PE. It is also important to recognize that the ranking of interventions by network meta-analysis may not be stable and may be susceptible to change with the addition of more studies; the ranking orders are also not supported by

evaluations of statistical significance. However, network meta-analysis findings were consistent with direct, pairwise comparisons of interventions to lower the risk of total DVT and major bleeding.

Further hampering evaluation of the trials, studies were not consistent in which specific outcomes were reported. Notably only total DVT was reported by more than 80 percent of the studies. However, as discussed, this outcome is of unclear clinical importance. Only about half of studies reported major bleeding, the adverse event of greatest concern for most interventions. Most of the VTE outcomes were reported by 50 percent or fewer of the studies. Only one study reported all VTE and adverse event outcomes of primary interest to our panel of stakeholders and only two studies reported all VTE outcomes. Full reporting of VTE outcomes and adverse events by trials would have allowed greater SoE for almost all intervention classes and several specific interventions. However, studies arbitrarily or selectively reported specific outcomes.

Our analyses did not find significant evidence of bias due to industry funding, based on subgroup meta-analysis comparisons of industry-funded vs. other studies. However, 54 percent of the trials were industry-supported and only 13 percent of RCTs explicitly reported no industry support, which might partially explain the selective outcome reporting (although, we did not find evidence of such an association).[25, 26] The relatively small number of RCTs available for meta-analysis for any given comparison and the small percentage of studies explicitly with no industry support meant that our analyses of industry funded required us to combine RCTs with no industry support and those that did not report funding source. If many of the studies that did not report funding were in fact industry-funded, then any real funding-source bias would have been diluted by the misclassification of funding source. Under the assumption that industry is most likely to fund and publish studies designed to be favorable to their products, the fact that the majority of evidence is industry-supported may explain the selective outcome reporting across studies (if favorable outcomes were more likely to be reported and nonfavorable outcomes omitted), the preponderance of evidence regarding enoxaparin, the sparseness of evidence on aspirin and mechanical devices, and relative sparseness of head-to-head trials of newer drugs (as opposed to comparisons with UFH or placebo).

The RCTs were generally consistent in regard to their eligibility criteria, mostly including all-comers without contraindications. This approach improves the applicability of the individual trials (and thus of the systematic review). Nonetheless, effect sizes in subgroups were rarely reported in these RCTs, and it greatly hampered our ability to evaluate potential explanations for heterogeneity or to hypothesize about possible subgroup differences based on patient history or surgery or anesthesia characteristics. Other than funding source, we were able only to evaluate potential differences between Asian and non-Asian studies. Overall, we found no significant difference between studies conducted in different regions (among analyzable studies), except major bleeding for the comparison of LMWH and FXaI in patients undergoing THR (summary OR in Asian RCTs 1.95, 95% CI 0.46 to 8.22; summary OR in non-Asian studies 0.68, 95% CI 0.49 to 0.94). Nevertheless, the event rates in the Asian studies were generally lower than the non-Asian studies. It suggests incomparability in the two populations besides ethnicity, which might explain the potential difference in the treatment effects. Only two RCTs reported on within-study subgroup analyses based on chronic kidney disease category (major bleeding, enoxaparin vs. desirudin) and by unilateral versus bilateral TKR surgery (DVT, aspirin vs. compression boots). Neither study found a significant difference in treatment effect in the different subgroups. Differences in effectiveness and safety between numerous different subgroups could not be evaluated due to lack of reporting of such analyses, including by age,

sex, race, thrombosis risk factors, bleeding risk factors, comorbidities, medication use, or surgery types or techniques.

Of note, this review evaluated the evidence as per the *a priori* protocol, which was built off of, and relied on, the 2012 VTE report.[13] Acknowledging that evidence for some interventions (e.g., mechanical devices) was likely to be sparse, we included larger NRCS. However, the smaller NRCSs that were excluded may have provided additional evidence, particularly for mechanical devices. While we did not reevaluate (mostly old) placebo-controlled RCTs among the direct comparisons between interventions, these studies were included in the NMAs. This review also did not cover numerous pertinent clinically important questions including comparisons of different strategies (e.g., aspirin and mechanical devices for low-risk patients and LMWH for high-risk patients). There are multiple standard methods for accounting for evidence in three (or more) arm studies in meta-analyses, when two (or more) of the arms are the same intervention (e.g., at different doses). In these instances, we chose the simplest method, which may be most clinically relevant in that we chose to analyze only the FDA-approved dose. When this was not possible, we selected the arm with the largest sample size (among FDA-approved or commonly used doses).

Future Research Recommendations

Much of the evidence base is insufficient to allow confident conclusions. Much of this lack is due to a relative sparseness of evidence evaluating interventions other than LMWH, and enoxaparin in particular. A more complete evidence base for the other treatments would allow for a stronger ranking of intervention classes, and of specific interventions, in term of risk of VTE and risk of major bleeding (and other adverse events). In particular, there is only sparse or low SoE data on the comparative effectiveness of aspirin or mechanical devices with LMWH or other anticoagulants. Given the likely low risk of major bleeding and other adverse events with aspirin and mechanical devices, it would be clinically important to determine whether patients at low risk of VTE events, in particular, could get adequate VTE prophylaxis with these low-risk interventions. Currently, there has been substantially more research conducted in patients undergoing THR than TKR; further studies regarding TKR may be warranted. In particular, few RCTs have been conducted in HFx surgery.

To avoid real and perceived bias (including, in particular concerns about reporting bias), ideally, a greater number of studies should be funded independently of industry. Furthermore, to minimize bias, all studies should report the full range of outcomes of interest, regardless of study results. Trial registration *in priori* and standard reporting compliant with Consolidated Standards of Reporting Trials (CONSORT) statement also help reduce potential reporting bias. For VTE prophylaxis studies, there is a fairly standard list of VTE and adverse event outcomes that are generally accepted as being of interest. This systematic review covers a complete list of outcomes that should be reported by all studies. To reduce the risk of bias in systematic reviews, all outcomes, particularly symptomatic DVT and PE and including those with no events, should be reported. However, to improve applicability of future studies to real-world clinical practice (where radiographic searches for asymptomatic DVTs are not performed), we would recommend that RCT protocols *not* mandate postsurgical diagnostic testing for asymptomatic DVTs.

This review made no assumptions about unreported event rates. Therefore, since mechanical device studies rarely reported bleeding (or other adverse event) outcomes, our pairwise and network meta-analysis review of mechanical devices had insufficient evidence about risk of bleeding. Ideally, all existing RCTs should report their full set of outcome results. This can

relatively easily be done by submitting trial results to a publicly-accessible registry such as ClinicalTrials.gov.

Larger RCTs should evaluate differences in treatment and adverse event effects in relevant subgroups of patients. Ideally, these analyses should be adequately powered. Based on our discussions with a panel of clinical experts and other key informants, the following subgroup analyses are of interest: sex, race/ethnicity, age, body weight, tobacco use, chronic disease, varicosities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. A small number of trials were explicitly limited to some of these subgroups (including no presurgical use of antithrombotics and unilateral surgery), the counterfactuals (e.g., only presurgical antithrombotics or bilateral surgery) have not been studied. Since it is unlikely that RCTs will focus on these rarer and higher-risk factors, it is more important for researchers to evaluate the subgroups within their studies, when available.

Conclusions and Clinical Implications

While a large body of RCT evidence exists on comparative effectiveness and harms of thromboprophylaxis interventions after major orthopedic surgery, none of the Key Questions are fully and adequately addressed. For most Key Questions, the evidence base was too sparse to allow conclusions with sufficient SoE. For the comparisons of different interventions classes, only selective pairs of intervention classes had sufficient evidence, but often only for selective outcomes. The largest body of evidence exists for THR, with fewer studies of TKR, and very few studies of HFx surgery. The large majority of head-to-head studies evaluated LMWH (enoxaparin, in particular) with relatively few studies evaluating other intervention classes. Only a small minority of studies reported no industry support. Studies did not regularly report on all VTE-related and adverse effect outcomes, resulting in important possible reporting bias. Studies mostly reported total DVT, an outcome with unclear clinical significance. Almost no studies reported subgroup analyses. These limitations restrict the conclusions that can be drawn from the body of evidence.

Based on head-to-head comparisons for which there is sufficient evidence to make conclusions, LMWH is more effective to prevent VTE outcomes (with moderate to high SoE) and safer to prevent major bleeding (moderate SoE) than UFH (in patients undergoing THR). There are tradeoffs between LMWH and DTI (for THR) such that DTI is more effective to prevent total and proximal DVTs (moderate SoE), but LMWH results in less major bleeding (low SoE). Similarly there are tradeoffs between LMWH and VKA (for TKR) such that LMWH is more effective to prevent proximal and total DVTs (low and high SoE, respectively), but VKA results in less major bleeding (low SoE). Based primarily on a very large, well conducted observational study (with propensity score analyses), there is low SoE that LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding after THR. Comparisons between LMWH and FXaI, and between other pairs of treatment classes, are inconclusive due to either conflicting evidence across specific types of VTE or different adverse events or because of insufficient direct comparative evidence.

Two other findings of note are that for both LMWH (in THR) and DTI (in TKR) there is variable SoE that higher dose LMWH or DTI is more effective to prevent DVT but lower doses result in less major bleeding. Evidence is insufficient regarding different doses of other drug

classes, different durations of treatment, comparisons of specific interventions, evaluations of combinations of interventions, and comparisons of timing of when to start thromboprophylaxis.

Of particular note, the inconsistent evidence LMWH versus FXaI was very likely due to selective outcome reporting. As an example, for THR, among 11 RCTs, only 6 reported on total VTE (favoring FXaI) and only 7 reported on symptomatic VTE (favoring LMWH), of which only 3 trials reported both outcomes. Selective outcome reporting was a major concern across all the analyses and in this case may have resulted in inconsistent conclusions across outcomes.

Due to a lack of sufficient direct comparisons between interventions for most outcomes of interest, we were able to construct network meta-analyses (to simultaneously evaluate both direct and indirect comparisons among all interventions) only for total DVT and major bleeding. For these outcomes network meta-analysis found that, for THR there is moderate SoE that FXaI is most effective to prevent total DVT; LMWH has lower risk of major bleeding that FXaI (low SoE). For TKR, by network meta-analysis we can conclude only that there is low SoE that FXaI is more effective to prevent total DVT than LMWH; there is insufficient evidence regarding major bleeding. Data are too sparse for HFx surgery to make conclusions from network meta-analysis. These analyses pertain to total DVT and major bleeding only.

In the face of incomplete and unclear evidence, patient and clinician preferences and values regarding the relative importance of avoiding VTE (primarily DVT) and major bleeding (and subsequent sequelae). While clinicians, policymakers, and clinical practice guideline developers should consider this evidence regarding relative effectiveness and safety of different thromboprophylaxis regimens (and its deficiencies), it is reasonable to also consider other sources of evidence not covered here (e.g., other observational research and assumptions related to mechanisms of action) to aid with decisionmaking in the face of incomplete evidence.

Future studies, particularly of interventions other than enoxaparin, are needed to address most Key Questions. These studies, and if feasible existing studies, should report all VTE-related and adverse event outcomes. Larger trials should conduct and report subgroup analyses of interest. Ideally, more future studies should be funded independently of industry to avoid real and perceived bias.

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Introduction

Background

Major orthopedic surgery carries a high risk for venous thromboembolism (VTE)—deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] The major orthopedic surgeries of greatest concern include total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries. PE, an obstruction of a pulmonary artery or its branches usually by an embolic thrombus, is potentially life-threatening and can result in chronic complications with generally poor prognosis, such as thromboembolic pulmonary hypertension.[2-4] DVTs are the principal intermediate process necessary for surgery-related PE and increase the risk of PE.[5] In addition, about 5 to 10 percent of patients with symptomatic DVTs develop severe postthrombotic syndrome, which may include venous ulcers, intractable edema, and chronic pain; although, these outcomes may take 10 years or more to develop.[6] Estimates suggest that in the contemporary era about 4.7 percent of patients undergoing major orthopedic surgery would have symptomatic VTE without prophylaxis.[1] Although, the rate of postoperative VTE is decreasing over time, likely due in part to a combination of more universal thromboprophylaxis and increasing use of early mobilization and decreased used of postoperative narcotics.

A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical devices.[1] Pharmacologic prophylactic treatments include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), antithrombin III-mediated selective factor Xa inhibitors, direct factor Xa inhibitors (FXaI), bivalent and univalent direct thrombin inhibitors (DTI), and antiplatelet agents (such as aspirin). Mechanical prophylaxis aims to minimize stasis, the principal putative factor resulting in venous thrombosis; it may also stimulate fibrinolysis, another mechanism to limit thrombosis. It can be dynamic and intermittent (e.g., intermittent pneumatic compression device [IPC]) or static (e.g., graduated compression stockings [GCS]). The modalities can be used alone or in combination, at variable doses (of drugs) or regimens (of mechanical devices; e.g., different pressure or compression frequency), and for different durations. However, prophylaxis with pharmacologic strategies also has important potential harms (risks) including major bleeding, prosthetic joint infections, and the need for reoperation, all of which may lead to major morbidities, death, permanent removal of the prosthetic joint, and increased hospital length of stay and costs.[7] Postoperative bleeding and hematoma formation are considered direct risk factors for the development of prosthetic joint infections.[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. Mechanical devices (when used alone), however, are thought to be inferior to pharmacological agents to prevent VTE.

VTE prophylaxis (or "thromboprophylaxis") is now standard of care for patients undergoing lower extremity major orthopedic surgery. Prophylaxis has been demonstrated to reduce the incidence of symptomatic and asymptomatic DVT (in comparison to placebo or no prophylaxis); however, because of rarity of postoperative PE,[1] the body of randomized controlled trial (RCT) evidence is not adequately powered to demonstrate the effect of prophylaxis on PE. The effect of prophylaxis on DVT risk reduction is generally considered an adequate proxy for likely PE risk reduction, but it remains unknown to what extent reducing the incidence of DVTs impacts the magnitude of any reduction in the incidence of PEs. This is particularly true for "total" DVT,

which includes both symptomatic and asymptomatic, and both distal and proximal, DVTs. Asymptomatic DVTs can be found only with diagnostic testing, which is done routinely only in the research study setting. The link between distal or asymptomatic DVTs and PEs is unclear. Nevertheless, avoiding DVT is a clinically worthwhile goal to reduce the incidence of lower extremity venous disease,[9] such as postphlebitic syndrome, venous insufficiency,[10, 11] and phlegmasia cerulean dolens (resulting in edema, pain, and gangrene).[12]

Scope

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery[13] (hereafter "the 2012 VTE report") addressed many of the uncertainties in this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing THR, TKR, or HFx surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in nonmajor orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 VTE report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence (SoE) that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical device VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical devices reduced the risk of VTE, including, specifically, DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical devices) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new FXaIs. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

We conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 VTE report. The surveillance review is summarized in the online protocol for this review.[14] Briefly, we screened and extracted basic data from abstracts found in PubMed from January 2010 to 16 July 2015. We evaluated the number and characteristics of studies—including RCT, nonrandomized comparative studies, systematic reviews, meta-analyses, and network meta-analyses—of potentially relevant articles. The updated literature search yielded 617 citations. Using the 2012 report's eligibility criteria, 160 articles were of potential interest (based on information available in their abstracts). Of these, 48 were existing systematic reviews, 49 were RCTs, 19 were pooling studies (meta-analysis or otherwise) of previous published or unpublished trials, and 44 were nonrandomized comparative studies (with at least 750 participants per study). We used this information to help determine the scope of the systematic review update. Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 Agency for Healthcare Research and Quality (AHRQ) report would be of greatest value. The panel included 10 members, including four orthopedic surgeons, two hematologists, one pulmonologist, one pharmacist, one physical therapist, and one nurse practitioner. Based on their input and the findings of the surveillance review, we focused the update on comparisons between specific prophylaxis interventions; different classes of interventions; different doses, regimens, and

treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

Several topics covered in the 2012 VTE report are not updated, including Key Questions related to "natural history" in patients not given thromboprophylaxis and incidence or predictors of VTE and comparing thromboprophylaxis to no thromboprophylaxis. In the modern era, it is rare for patients to not have some form of thromboprophylaxis; therefore, this question is of less clinical interest, and it is unlikely that there will be substantial new evidence regarding these topics. Therefore, these topics (regarding no prophylaxis) are not updated. We also do not update the Key Question evaluating DVT as a proxy (or predictor) for PE, as no new evidence was expected. Finally, all questions related to orthopedic surgeries other than TKR, THR, and HFx surgery are not updated, since only very limited new studies were found during the surveillance review; thus, conclusions and SoE are unlikely to change compared to the 2012 VTE report.

The objectives for the systematic review are to update the 2012 VTE report focused on the comparative effectiveness (for VTE outcomes and harms) of different thromboprophylaxis interventions for patients undergoing major orthopedic surgery (THR, TKR, and HFx surgery).

Key Questions

The following are the Key Questions (KQs) addressed by the review:

KQ 1 (update of original KQ 5): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of thromboprophylaxis interventions on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 2 (update of original KQ 6): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual thromboprophylaxis interventions within classes (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 3 (new KQ based on original KQ 8): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of different doses, regimens, or treatment durations of the same thromboprophylaxis interventions (low molecular weight heparin, factor Xa inhibitors, direct thrombin inhibitors, and mechanical devices) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 4 (update of original KQ 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

KQ 5 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), based on network meta-analysis, what are the comparative effects of thromboprophylaxis interventions on deep vein thrombosis and, separately, major bleeding?

5.1: What are the comparative effects of different classes of thromboprophylaxis interventions?

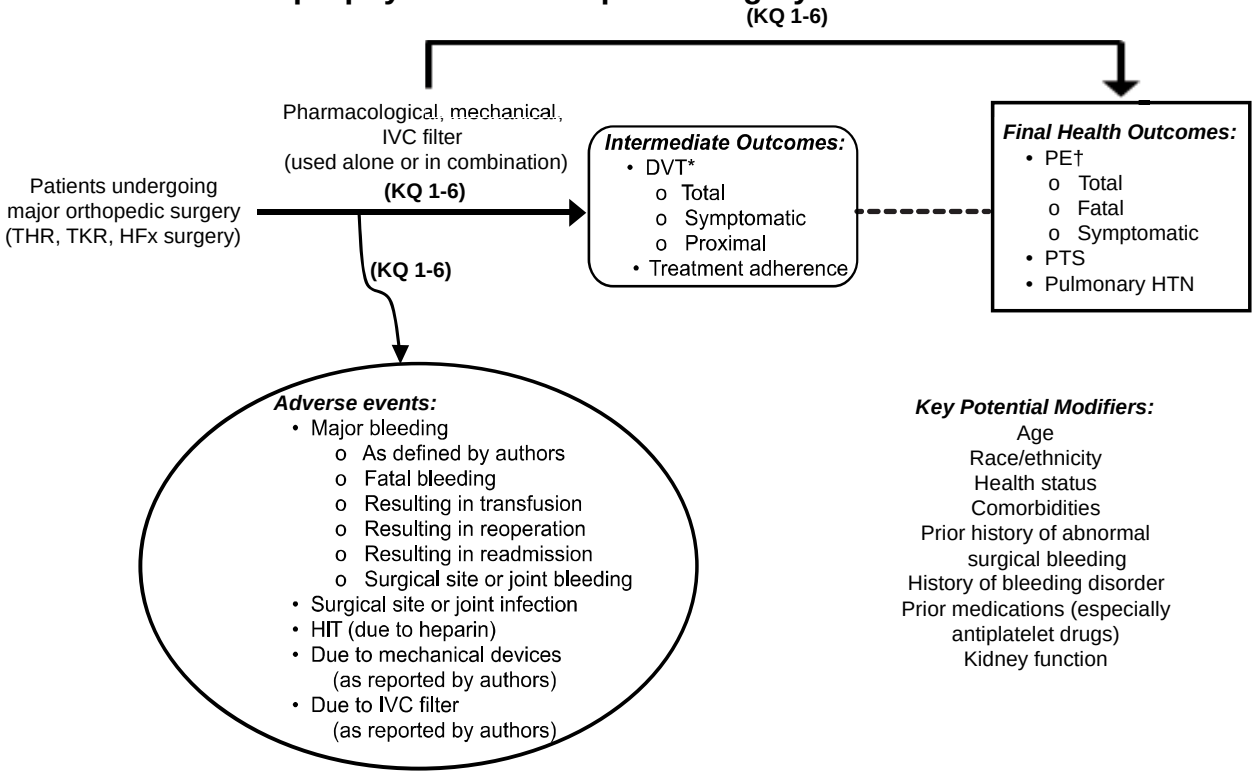
5.2: What are the comparative effects of different individual thromboprophylaxis interventions?

KQ 6 (new KQ): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of starting pharmacologic thromboprophylaxis at different times (i.e., preoperative, intraoperative, postoperative) on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

Analytic Framework

To guide the assessment of studies that examine the effect of thromboprophylaxis on final, intermediate, and adverse outcomes in patients undergoing major orthopedic surgery the analytic framework maps the specific linkages associating the populations of interest, the interventions, modifying factors, and outcomes of interest (Figure 1). The analytic framework depicts the chains of logic that evidence must support to link the studied interventions studied.

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



Abbreviations: DVT = deep vein thrombosis, HFx = hip fracture, HIT = heparin-induced thrombocytopenia, IVC = inferior vena cava, KQ = Key Question(s), PE = pulmonary embolism, PTS = postthrombotic syndrome, Pulmonary HTN = pulmonary hypertension, THR = total hip replacement, TKR = total knee replacement, VTE = venous thromboembolism

* DVTs are the principal intermediate outcomes necessary for surgery-related PE or postthrombotic syndrome. Total DVTs (asymptomatic and symptomatic, or alternatively, proximal and distal) are of interest because, conceptually, all DVTs may result in PE or postthrombotic syndrome; although, symptomatic DVTs are believed to be a higher risk factor for postthrombotic syndrome and proximal DVTs are believed to be a higher risk factor for PE, particularly fatal PE. Asymptomatic and distal DVTs are not included in the list of DVTs of interest, since they are subsumed by total DVT and are not of great clinical interest alone. Of note, it would be equally reasonable to consider DVTs, especially symptomatic DVTs, to be final health outcomes.

† Total PEs includes both symptomatic and asymptomatic PEs, or alternatively, fatal and nonfatal PEs. Asymptomatic and nonfatal PEs are not included in the list of PEs of interest, since they are subsumed by total PE and are not of great clinical interest alone.

Methods

The present review updates and refines the 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery.[13] It focuses on the Key Questions (KQ) listed at the end of the Introduction. Briefly, it evaluates the comparative effectiveness of different thromboprophylaxis modalities or interventions, not including placebo or no thromboprophylaxis, in patients undergoing major orthopedic surgery—total knee replacement (TKR), total hip replacement (THR), and hip fracture (HFx) surgeries—to prevent venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT) and to minimize major complications, particularly bleeding.

The Brown Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature, using established methodologies as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[15]

Topic Refinement and Review Protocol

We conducted a surveillance review of the literature since the last search of the 2012 VTE report and discussed our findings with a Technical Expert Panel (TEP) and local domain experts. The TEP provided a range of insights to allow us to refine the KQs, eligibility criteria, and protocol, and regarding the currency and relevance of the 2012 VTE report and its KQs and eligibility criteria. The TEP included 10 members, including four orthopedic surgeons, two hematologists, one pulmonologist, one pharmacist, one physical therapist, and one nurse practitioner. The panel included committee members from the American Academy of Orthopaedic Surgeons clinical practice guidelines, committee members from the American College of Chest Physicians clinical practice guidelines, and an author of the 2012 VTE report.

Upon revision of the KQs for the updated systematic review, the TEP provided input to help refine the protocol, identify important issues, and define parameters for the review of evidence. The TEP was also asked to suggest additional studies for evaluation.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the KQs that have been published since the 2012 VTE report, which included studies published from 1980 through May 2011. We searched PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and Embase® databases. Searches were limited to January 2010 through June 3, 2016, which included an overlap of more than 1 year with the search done for the 2012 VTE report. The updated literature searches replicated the searches from the 2012 VTE report and added additional terms for new treatments (factor Xa inhibitors [FXaI]). See Appendix A for the complete search strategy. The search strategy was peer reviewed by an independent, experienced information specialist/librarian.

We also searched the ClinicalTrials.gov registry and the Food and Drug Administration, Healthy Canadians, and the U.K. Medicines & Healthcare products Regulatory Agency Web sites for relevant documents from 2011 through July 18, 2016. In addition, the reference lists of published clinical practice guidelines, systematic reviews, and Scientific Information Packages from manufacturers were hand-searched, and the TEP members were invited to provide references of new studies. Existing systematic reviews were used primarily as sources of new studies. With the exception of studies included in the 2012 VTE report, we extracted and

incorporated any studies *de novo* and did not summarize or incorporate the existing systematic reviews. All articles identified through these sources were screened for eligibility using the same criteria as was used for articles identified through literature searches.

All studies cited and tabulated in the 2012 VTE report were screened for eligibility on a par with new studies. However, as noted below, we relied on the summary tables in the 2012 VTE report for data from these studies.

Study Eligibility Criteria

The eligibility criteria for this update are mostly similar to the criteria used in the 2012 VTE report, as pertain to updated KQs.

Populations of Interest

For all KQs, studies of patients undergoing major orthopedic surgery (THR, TKR, HFx) were eligible. In contrast with the 2012 VTE report, we excluded studies that included more than one type of surgery but did not report results separately by surgery type. This modification was implemented in part for clarity and precision across the three substantially different surgeries and also because of indications of different risks of VTE and major bleeding for the different surgeries, as suggested by the 2012 VTE report (total DVT on placebo: THR 39%, TKR 46%, and HFx surgery 47%; major bleeding on placebo: THR 1%, TKR 3%, and HFx surgery 8%).[1] We did not exclude studies based on details regarding the type of eligible surgery, related anesthesia management, or perioperative care. Therefore, for example, both primary and revision arthroplasty and unicompartmental and tricompartmental TKR are included. Subpopulations of interest included those defined by specific surgery, age, race/ethnicity, health status, comorbidities, prior history of abnormal surgical bleeding or bleeding disorder, prior medications (e.g., antiplatelet drugs), kidney function, and treatment adherence/compliance.

Interventions of Interest

The interventions of interest for all KQs included pharmacological VTE prophylaxis agents within the defined classes of antiplatelet agents, low molecular weight heparin (LMWH), unfractionated heparin (UFH), factor VIII inhibitors (FEI), factor Xa inhibitors (FXaI), factor XI inhibitors (FXIi), direct thrombin inhibitors (DTI), vitamin K antagonists (VKA), and mechanical VTE prophylaxis devices within the classes graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC), and venous foot pumps (VFP). We also included studies of prophylactic inferior vena cava filters for KQs 1 and 5 (that compared classes of interventions). We included multimodality therapies KQ 3 (different doses, regimens, or treatment durations). We included studies of combination therapies (e.g., drug plus mechanical device) for KQs 4 and 5 and of different starting times relative to surgery for KQ 6.

Comparators of Interest

We included any of the above interventions as comparators as pertinent, including

- KQ 1, 5 intervention in a different class (and placebo for KQ 5)
- KQ 2, 5 intervention within the same class (and placebo for KQ 5)
- KQ 3 same intervention with different (lower) dose (or anticoagulation goal), (less intensive) regimen, or (shorter) duration
- KQ 4 single modality intervention

- KQ 6 same intervention started at different (later) time relative to surgery

There is an important caveat regarding KQ 5, the network meta-analyses. In contrast to other KQs, we included placebo and no thromboprophylaxis study arms. This was done to enhance the power of the network meta-analysis. See below, under Study Design, regarding where no treatment arm data were derived.

Outcomes of Interest

For all KQs, except KQ 5 (the network meta-analysis), we evaluated the outcomes in the following list. We did not use strict *a priori* definitions of the outcomes, but included all reported outcomes as defined by study researchers. When necessary, we used our best judgment to categorize outcomes when studies failed to clearly define their reported outcomes (e.g., whether reported DVTs were total or symptomatic, whether reported bleeding was major).

- VTE (combined PE and DVT)
    - Total VTE (symptomatic and asymptomatic)
    - Symptomatic VTE
- PE
    - Total PE (fatal and nonfatal; symptomatic and asymptomatic)
    - Fatal PE
    - Symptomatic PE
- DVT
    - Total DVT (symptomatic and asymptomatic; proximal and distal)
    - Symptomatic DVT
    - Proximal DVT
- Postthrombotic syndrome (PTS)
- Pulmonary hypertension (due to PE)
- Adherence (compliance) with treatment
- Adverse events due to intervention(s)
    - Major bleeding, including:
        - Fatal bleeding
        - Bleeding leading to transfusion
        - Major bleeding leading to reoperation
        - Major bleeding leading to readmission
        - Surgical site / joint bleeding
        - Bleeding leading to infection
        - As defined by authors
    - Surgical site/wound-related infections
    - Surgical site/wound complications (other than bleeding, infection)
    - Heparin-induced thrombocytopenia
    - Adverse events due to mechanical devices (as reported by authors)
    - Adverse events due to IVC filter (as reported by authors)
    - Other clinically significant adverse events reported by studies

For KQ 5 (the network meta-analysis), we fully evaluated only *total DVT* and *major bleeding*.

We included confirmed and unconfirmed VTE, but downgraded the risk of bias for those studies that analyzed unconfirmed VTE. If both confirmed and unconfirmed VTE were reported, we extracted only the confirmed VTE data. Other outcomes were considered but had insufficient evidence for network meta-analysis; however, they are described briefly in Appendix H.

Study Design

For all KQs, we included randomized controlled trials (RCT) of any sample size. For KQs other than the network meta-analysis (KQ 5), we also included prospective or retrospective nonrandomized comparative studies (NRCS) with at least 750 patients per surgery type, per study. In contrast to the 2012 VTE report, we also required at least 50 patients in each included study arm (or intervention). NRCSs with fewer than 50 patients in any study arm (per surgery type) were still eligible if they compared at least two study arms with 50 or more patients and had 750 or more patients in the remaining study arms; however, the study arms with less than 50 patients were omitted from analysis.

We included published, peer-reviewed articles, conference abstracts and presentations, and studies reported only in the ClinicalTrials.gov Web site. Non-English language publications were extracted by researchers fluent or facile in the published languages. Unavailable publications were included and extracted only from their English language abstract.

Timing

We included studies with any duration of followup. For VTE outcomes, we extracted results at all reported timepoints, but for meta-analyses we preferentially analyzed timepoints closest to 30 days postoperative (as being the most commonly reported timepoint).

Setting

Studies performed in hospital (with or without continuation of intervention or followup after discharge)

Study Selection

We assessed titles and abstracts of citations identified from literature searches for inclusion, using the above eligibility criteria. Abstract screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the eligibility criteria. Both abstract and full-text screening was conducted in duplicate with conflicts resolved by reconciliation among the whole research team. All rejected full-text articles were confirmed by the project lead.

Studies included in the 2012 VTE report were reassessed for inclusion based on the summarized data available in the 2012 VTE report. In general, we did not confirm eligibility criteria for these studies from the full-text articles.

Data Extraction

Each study was extracted by one methodologist and confirmed by at least one other experienced methodologist. Disagreements were resolved by open, free-flowing discussion among the team to achieve consensus. Data extraction was conducted into customized forms in

the Systematic Review Data Repository online system designed to capture all elements relevant to the KQs (http://srdr.ahrq.gov); the completed extraction forms are available for public review at this site. These included population characteristics, including description of patients' surgery, descriptions of the interventions analyzed, descriptions of relevant outcomes, sample sizes, study design features, funding sources, results (including adverse events), and risk of bias assessment. The forms were tested on several studies and revised as necessary.

New studies added to the 2012 VTE report were extracted from the full-text articles and any available supplemental material. With few exceptions, eligible studies from the 2012 VTE report extracted and entered into SRDR based only on the available data presented in the 2012 VTE report.

Risk of Bias Assessment

We based the methodological quality of each study on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[16] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used selected questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up.[17] The methodological quality of the eligible studies from the 2012 VTE report was based solely on what was reported in that report's methodological quality tables. Risk of bias questions included in the current review that were not assessed in the 2012 VTE report were marked as "NR" (not reported).

Data Synthesis

Narrative and Tabular Synthesis

All included studies are presented in summary tables that include the important features of the study populations, design, intervention, and risk of bias. Study results are summarized in two ways, depending on the available evidence across studies. For specific comparisons that were analyzed by pairwise meta-analysis, results are reported graphically (in forest plots). For specific comparisons, for which pairwise meta-analysis was not appropriate or feasible (i.e., not conducted), outcome results are tabulated in Appendix F and summarized in high-level summary tables. Analyses with sufficient evidence for meta-analysis (including network meta-analysis) are described in the text. Other comparisons with inadequate evidence (for meta-analysis and from the perspective of strength of evidence [SoE]) are summarized more generally. All outcome results are available in SRDR and is publically available (http://srdr.ahrq.gov).

Pairwise Meta-Analysis

For KQs 1 through 4 and 6, we conducted restricted maximum likelihood random effects model meta-analyses of four or more comparative studies that were sufficiently similar in population, interventions, and outcomes. Odds ratios (ORs) were chosen as the metric to analyze categorical outcomes. In the analysis of rare outcomes (<1%), we used Peto's OR.[18-20] Studies with no events in both trial arms were excluded as they do not contribute to the estimate of the summary effect. In the analysis by class (KQ 1), for trials containing arms with different doses of the same intervention, we included the arm with the dose that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention.

Pairwise meta-analyses were conducted in R using the *metafor* package. Results are presented in terms of summary ORs and the corresponding 95 percent confidence interval (CI).

Network Meta-Analysis

To address KQ 5, we conducted network meta-analyses under a Bayesian framework. The specific model is described by Dias et al.[21] Network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct comparisons (where interventions are compared head-to-head) and indirect comparisons (where interventions are compared through other reference interventions). Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that there is consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is similar across trials, and thus, patients are similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons (where the direct and indirect comparisons contradict each other).

For binary outcomes (e.g., total DVT and major bleeding), the network meta-analysis model corresponds to a generalized linear mixed model with a logit link. We included random effects on the treatment parameters, which allowed each study to have a different but related treatment effect estimate versus a reference treatment. The amount of between-study variance (heterogeneity) was assumed to be constant across all treatment comparisons. We used noninformative prior distributions for the model parameters. The models initially discarded a set of 50,000 iterations as "burn-in," and the inferences were based on additional 50,000 iterations ("runs") using 4 chains. Convergence of the chains was assessed by the Gelman-Rubin statistic and visual inspection of trace plots. Due to the sparseness of data in some networks, we also conducted analyses with an informative log-normal prior for the heterogeneity parameter.[22] The results of these analyses lead to similar conclusions as the base analysis, and are presented in Appendix G.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach.[21] This approach evaluates each treatment comparison in terms of its direct and indirect evidence estimates. Discrepancies between these estimates indicate inconsistency. Since we did not find any evidence of inconsistency, only results from the (consistency) network meta-analysis are presented. However, the inability of the models to detect inconsistency in our evidence base with sparse data may be due to the lack of power rather than suggestive of consistent networks.

We conducted a total of 12 network meta-analyses to compare all treatment alternatives across studies. For each of three surgeries (THR, TKR, and HFx surgery) and for the two outcomes (total DVT and major bleeding) we conducted two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., LMWH, antiplatelet drugs) and 2) comparisons of individual interventions. For trials containing arms with different doses of the same intervention, we included the arm with the dose that was most similar to other studies or the arm with the largest sample size in the event that it was the only study of that intervention. For all network meta-analyses (in contrast to KQ 1-4 and 6), we included placebo/no treatment as an intervention (or class) to strengthen the network of evidence. Placebo-controlled trials were included in the network if they included active interventions that were otherwise in the network. We omitted

placebo-controlled trials that would be a spur in the network (if, across trials, the intervention was compared only to placebo, not to any active intervention). Network meta-analyses were conducted in R using the *gemtc* package. Results are presented in terms of summary ORs and the corresponding 95 percent credible interval (CrI).

Summarizing Findings Across Studies

For each comparison of interventions, we determined a conclusion (or summary of findings across studies) for each outcome with sufficient evidence (i.e., not insufficient evidence, see *Grading the Strength of Evidence*).

We concluded the evidence "favors" one intervention (over the other) when

- there was a statistically significant difference by meta-analysis,
- when the preponderance of studies found a statistically significant difference in the same direction (when no meta-analysis was conducted), or
- meta-analysis found a statistically nonsignificant effect size that was either greater than 1.20 or less than 0.80.
    - However, if the 95 percent confidence interval was highly imprecise (beyond *both* 0.50 and 2.00), the conclusion was "unclear" regardless of the magnitude of the point estimate.
    - If a conclusion was based on a statistically nonsignificant effect size, the strength of evidence (see below) was low (it could not be moderate or high).

We concluded that interventions had similar effects (noted in tables as favoring "either") when summary effect sizes (by meta-analysis) or the preponderance of studies' effect sizes (when not meta-analyzed) were between 0.80 and 1.20, were not statistically significant, and were not highly imprecise or inconsistent (across studies).

When studies were sparse, effect size estimates were highly imprecise (95% confidence intervals beyond *both* 0.50 and 2.00, usually due to sparse events), or studies were highly inconsistent (e.g., with point estimates ranging from 0.14 to 3.03), we deemed the findings to be "unclear" (with an insufficient strength of evidence).

Subgroup Analyses and Metaregression

All studies were evaluated for within-study subgroup (or predictor) analyses. As feasible, studies were also categorized based on whether, as a whole, they evaluated particular populations of interest, such as studies that included at least 90 percent of a subgroup of interest, including sex, race/ethnicity, older age group, body weight category, tobacco use, chronic disease, varicosities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, primary versus revision surgery, use of cemented fixation, tourniquet use, tranexamic acid use, anesthesia type, etc. We also investigated potential differences between studies based on industry funding and study region (Asia vs. other). We aimed to conduct random effects model metaregressions for many variables but data were too sparse to allow meaningful analyses for most.

Grading the Strength of Evidence

We graded the strength of the body of evidence as per the AHRQ Methods Guide on - assessing the SoE.[23] We assessed the SoE for each health outcome, as determined with input

from the panel of technical experts: total VTE, symptomatic VTE, PE, DVT, and adverse events. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Throughout the report, all estimates with 95 percent CI or CrI beyond 0.5 and 2.0 were considered to be highly imprecise. Based on these assessments, we assigned a SoE rating as being either high, moderate, low, or there being insufficient evidence to estimate an effect. Conclusions based on statistically nonsignificant findings could have at best a low SoE. Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one or two studies were deemed to have insufficient evidence to allow for a conclusion (with the exception that particularly large, generalizable single studies could provide at least low SoE). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a "Strength of Evidence" table detailing our reasoning for arriving at the overall SoE rating.[20]

Peer Review

A draft version of this report was reviewed (from July 27 to August 23, 2016) by invited and public reviewers, including representatives from orthopedic societies, industry, our TEP, and the general public. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The Results chapter is organized first by Key Question, then by surgery—in the following order: total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgery. Subsequently, results are ordered by comparison in alphabetical order. Comparisons with no evidence (no studies) are omitted. Outcomes are reported in three categories, as follows: 1) venous thromboembolism (VTE) related outcomes—including VTE, pulmonary embolism (PE), deep vein thrombosis (DVT), and other VTE-related outcomes (postthrombotic syndrome [PTS] and pulmonary hypertension [HTN]); 2) adverse events, including major bleeding, other bleeding, serious adverse events (study-defined combinations of adverse events), and other adverse events; and 3) adherence. Specific outcomes not reported within each intervention comparison section had no data.

Appendix A presents the literature search strategies (for each searched database). Appendix B lists the articles that were reviewed in full text that were excluded, with their rejection reasons. Appendix C presents the study-level risk of bias assessments of all studies (divided by surgery type for randomized controlled trials [RCT] and then for all nonrandomized comparative studies [NRCS]). Appendix D presents study-level study design and baseline data (divided as in Appendix C). Appendix E presents study-level intervention arm details (also divided as in Appendix C). Appendix F presents study-level results details.

Summary of Studies

The literature searches yielded 1738 citations (Figure 2). We rescreened 118 studies included in the 2012 VTE report and 107 references found in relevant existing systematic reviews. Of these, 455 articles were screened in full text, of which 313 were excluded for the reasons listed in Figure 2 and Appendix B. The 142 studies included 127 RCTs and 15 NRCSs; they provided 85 studies of THR, 60 of TKR, and 12 of HFx surgery. The publication status and sources of the studies are listed in Figure 2. The grey literature searches added two studies, both unpublished reports with results in ClinicalTrials.gov.

Studies evaluated the following thromboprophylaxis classes (and combinations thereof): antiplatelet drugs, direct thrombin inhibitors (DTI), factor VIII inhibitors (FEI), factor Xa inhibitors (FXaI), factor XI inhibitors (FXIi), low molecular weight heparin (LMWH), mechanical devices, unfractionated heparin (UFH), and vitamin K antagonists (VKA). The studies evaluated the following specific interventions (and combinations thereof): aspirin (antiplatelet drug); dabigatran and desirudin (DTIs); TB402 (FEI); apixaban, darexaban, edoxaban, eribaxaban, fondaparinux, rivaroxaban, and TAK422 (FXaIs); factor XI antisense oligonucleotide (FXIASO; FXIi); dalteparin, enoxaparin, semuloparin, and tinzaparin (LMWHs); flexion devices, graduated compression stockings (GCS), intermittent pneumatic compression (IPC), and venous foot pumps (VFP) (mechanical devices); UFH; and warfarin (VKA).

We chose the principal outcomes for this review (the various VTE outcomes, major bleeding, and serious adverse events) based on an *a priori* determination of their importance in regards to thromboprophylaxis choice decisionmaking and the high likelihood that these outcomes would be available to researches of almost all RCTs. However, only total DVT was reported by more than 80 percent of the studies (82%), an arbitrary threshold we chose to suggest high risk of reporting bias. In descending order, the remaining principal outcomes were proximal DVT (66% of studies reported), total PE (52%), major bleeding (52%), fatal PE (48%), symptomatic DVT

(40%), symptomatic VTE (18%), symptomatic PE (17%), total VTE (15%), and study-defined serious adverse events (11%).

Of note, almost all studies that reported serious adverse events did not define the outcome. Presumably, it included major bleeding, but this is not clear. Two studies described them as treatment-related events that lead to death, are life-threatening, require or prolong hospitalization, cause disability or incapacity, jeopardize the subject, or require an intervention.[24, 25] One study referred to "standard regulatory definitions", but did not further define.[26]

Randomized Controlled Trials

Among the RCTs, 61 (50%) reported industry funding, 4 (3%) used materials supplied by industry, 18 (15%) explicitly reported no industry support, and 40 (33%) did not provide funding information (Appendix D).

In general, for the RCTs the risk of bias was low regarding randomization, allocation concealment, group similarity at baseline, and methods used for outcome assessment. Reporting, compliance with interventions, timing of outcome assessment, and definition of adverse effects were explicitly reported in fewer than half of the RCTs. Fifty-two RCTs had a high risk of bias regarding blinding of patients (in addition, 16 had unclear risk of bias, 1 not reported from the original report[a]), 51 for blinding of health care providers (25 unclear, 1 not reported from the original report), and 20 for blinding of outcome assessors (29 unclear). Twenty-eight RCTs had a high risk of bias in compliance of intention-to-treat principle in data analysis (8 unclear). Attrition bias was rated high in 22 RCTs (10 unclear). A full list of risk of bias evaluation is available in Appendix C.

Nonrandomized Comparative Studies

Overall, we included 15 NRCSs. Five NRCSs evaluated only THR,[27-31] six only TKR,[32-37] three had separate analyses of THR and TKR,[38-40] and one evaluated HFx surgery.[41] Two reported industry funding,[36, 40] 12 explicitly reported no industry support,[27-35, 37, 39, 41] and in one it was not reported (Appendix D).[38] In general, the risk of bias was low for incomplete results reporting (2 unclear) and timing of outcome assessments (3 unclear). One NRCS had high risk of bias for adverse event reporting and one was unclear. Similarly, one NRCS had high risk of bias for compliance with interventions and a second was unclear. One NRCS had high risk of bias for patient selection, and a second was unclear. Seven NRCSs had high risk of bias for group similarity at baseline (4 unclear); five for assessment of outcomes (4 unclear). Seven NRCSs had high risk of bias for blinding of outcome assessors, and another five were unclear. Eight had high risk of bias for selective outcome reporting. Full risk of bias evaluations are in Appendix C.

Correlation of DVT and PE Across Trials

To help put the VTE outcomes into context, we performed simple correlation analyses of rates of DVT (proximal, symptomatic, and total) and of PE (fatal, symptomatic, and total) across studies and interventions, including placebo. Analyses were run excluding studies arms with no DVT or PE events; more than half the studies that reported PE outcomes had no PE events. We also excluded studies with atypically high rates of PE (i.e., outlier studies that typically

[a] The current review assessed risk of bias domains not consistently addressed by the 2012 VTE report. We did not assess these studies for these risk of bias domains, but instead marked them as "not reported".

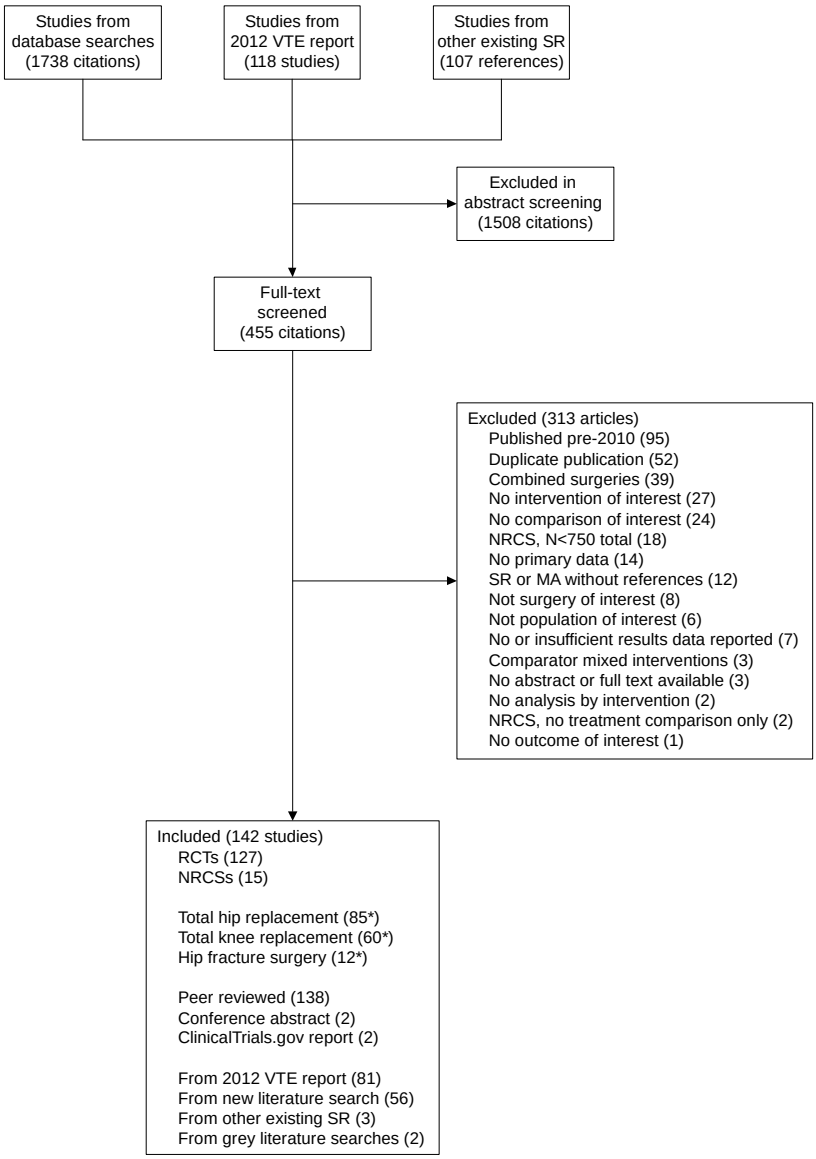
represented single events in small studies). Across studies, rates of total PE (the most commonly reported PE outcome) were correlated with symptomatic DVT (r=0.57), but not distal or total DVT ($|r| \leq 0.10$). Rates of symptomatic PE were correlated with rates of proximal DVT (r=0.33) but not symptomatic DVT (r=0.19). Fewer than five studies reported (non-zero) fatal PE events or both symptomatic PE and total DVT, so correlations were not assessed for associated pairs of outcomes. In summary, the rates of the most commonly reported PE and DVT outcomes (total PE and total DVT) are not correlated within these studies; however, rates of symptomatic DVT are correlated with rates of total PE across studies.

Subgroup Analyses

Only two of the RCTs reported subgroup analyses. These are reported in the appropriate sections, based on the Key Question, surgery, and intervention comparison. We collected data to conduct metaregressions across studies based on different population characteristics as listed in the Methods section (under *Subgroup Analyses and Metaregression*). However, overall, studies were generally homogeneous in regard to study eligibility criteria (within surgical types). Almost all studies included all-comers and did not restrict eligibility based on patient or surgery characteristics. Some studies excluded patients with a bleeding history or chronic VKA or antiplatelet drug use, but the counterfactuals (studies that included only patients with a bleeding history or on chronic antithrombotic drugs) were rare or nonexistent. Therefore, analyses across studies of different subgroups were not productive.

For comparisons with at least six studies that could be meta-analyzed (that evaluated the same surgery and the same class or intervention comparison), we conducted metaregressions if at least one of the studies differed in a study-level covariate. Based on the available data, we thus conducted metaregressions for differences in funding source (industry vs. other funding source) and geography (Asian vs. non-Asian study). This latter comparison was conducted due to a perception that risks of VTE and adverse effects may differ in Asian populations.[42]

Figure 2. Literature flow



Abbreviations: MA = meta-analysis, N=sample size, NRCS = nonrandomized comparative study, RCT = randomized controlled trial, SR = systematic review, VTE = venous thromboembolism.

* Sums to more than 142 since some studies reported different surgeries separately.

Key Question 1: Comparison of Thromboprophylaxis Intervention Classes

Note that network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Question 1: Total Hip Replacement

The results summary table (Table 1) includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 1 (THR): Antiplatelet Drug Versus VKA

Two RCTs (N=274) and one NRCS (N=887) compared an antiplatelet drug to a VKA;[31, 43, 44] in one RCT a mechanical device was used in all patients. One RCT reported on total and proximal DVTs; the other reported total PE and proximal DVTs. In all analyses, there was no significant difference between intervention classes. The NRCS found a higher rate of bleeding events in the VKA group compared to the antiplatelet group (1.7% vs. 0.3%), without statistical analysis (Appendix Table F4).[31] Neither study reported on adherence.

Key Question 1 (THR): Antiplatelet Drug Versus Mechanical Device

A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between aspirin and mechanical devices (OR 1.41, 95% CI 0.37 to 5.34), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F4).[29]

Key Question 1 (THR): DTI Versus FXaI

One RCT compared DTI versus FXaI, in which all patients were also treated with LMWH.[45] The study reported only on total DVT, finding no difference between the two intervention classes.

Key Question 1 (THR): DTI Versus UFH

Two RCTs (N=999) compared DTI versus UFH.[46, 47] Both studies found no significant differences in total PE events and neither reported a fatal PE event. Both found statistically significant differences in total and proximal DVTs, favoring DTI (total DVT: OR 0.26 [95% CI 0.13 to 0.50] and 0.44 [95% CI 0.28 to 0.69]; proximal DVT: OR 0.13 [95% CI 0.05 to 0.31] and 0.18 [95% CI 0.05 to 0.62]).

Neither study reported a fatal bleed. One study found no significant difference in bleeding leading to reoperation and one had no such events. One study found no significant difference in surgical site bleeding. Both studies found no significant difference in 30-day mortality.

Neither study reported on adherence.

Key Question 1 (THR): FEI Versus FXaI

One RCT (N=415) compared FEI versus FXaI.[48] The study found no significant difference in rates of total VTE, total DVT, and proximal DVT, but no events in either arm for symptomatic VTE, fatal PE, symptomatic PE, or symptomatic DVT.

The study found no significant difference in rate of major bleeding but significantly more surgical site bleeding with FEI. There was no significant difference in 30-day mortality.

The study did not report on adherence.

Key Question 1 (THR): LMWH Versus Antiplatelet Drug

Two NRCSs compared LMWH with an antiplatelet drug (Appendix Table F4).[28, 29] Both evaluated total PE. One very large study found identical rates of PE among 85,642 patients given

LMWH and 22,942 patients given aspirin (0.68%)[28]; adjusted OR = 0.97, 95% CI 0.81 to 1.17; propensity-adjusted OR [in a matched subset] = 0.94, 95% CI 0.75 to 1.17, P=0.56). The second smaller study (N=1533) found a higher PE rate in the antiplatelet drug group (1.7%) than the LMWH group (0.2%), without statistical analysis.[29] The large NRCS also found no significant difference in symptomatic (diagnosed) DVT that somewhat favored LMWH (LMWH 0.94%, aspirin 0.99%; adjusted OR = 0.91, 95% CI 0.79 to 1.06; propensity-adjusted OR [in a matched subset] = 0.84, 95% CI 0.70 to 1.03 favoring LMWH, P=0.10) and no difference in major bleeding events, defined as cerebrovascular accident or gastrointestinal hemorrhage (LMWH 0.72%, aspirin 0.77%; adjusted OR = 0.92, 95% CI 0.77 to 1.09; propensity-adjusted OR [in a matched subset] = 0.95, 95% CI 0.77 to 1.17, P=0.63).

Key Question 1 (THR): LMWH Versus DTI

Four RCTs (N=6900) compared LMWH versus DTI.[49-52] All reported on VTE-related outcomes.

VTE Outcomes

No VTE-related outcome was analyzed by more than three RCTs. One study found no significant difference in symptomatic VTE.[50] Two studies found no significant differences in total PEs or fatal PEs (one study had no fatal PE events).[49, 51] Three studies analyzed total DVT; all found more total DVTs with LMWH, but the difference was statistically significant in only one study (range of ORs 1.14 [95% CI 0.79 to 1.64] to 1.52 [95% CI 1.19 to 1.94]).[49, 50, 52] The same three studies found similar results for proximal DVT (range of ORs 1.35 [95% CI 0.53 to 3.42] to 1.89 [95% CI 1.04 to 3.44]). Two of the studies found no significant difference in symptomatic DVT events.[49, 50, 52]

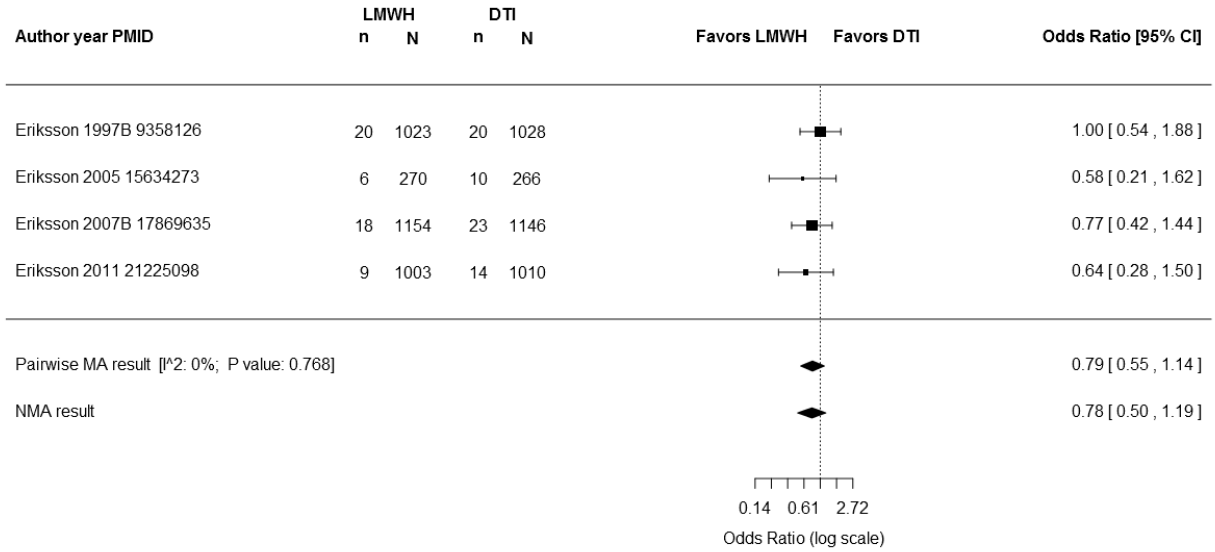
Major Bleeding

Four RCTs (N=6900) that compared LMWH and DTI reported major bleeding (0.9% to 2.2% in LMWH, 1.4 to 3.8% in DTI).[49-52] The rate was lower in the LMWH group in three RCTs.[50-52] Meta-analysis of the four RCTs found no significant difference between the two drug classes for the risk of major bleeding (summary OR=0.79; 95% CI 0.55 to 1.14). Study results were homogeneous (I^2 = 0%, P = 0.77) (Figure 3).

Subgroup Analysis

One RCT reported results for serious bleeding by level of chronic kidney disease.[49, 53] Event rates were low for all participants (2% in both the enoxaparin and desirudin arms). They reported that for chronic kidney disease category 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.11). For chronic kidney disease category 3A (n=758), the rates were the same (0.3% in both arms). For chronic kidney disease categories 1-2 (n=700), DVT rates were also lower in the enoxaparin arm (0.6% vs. 0%).[53]

Figure 3. Forest plot: Total hip replacement, major bleeding, LMWH versus DTI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Two RCTs evaluated fatal bleeding;[50, 51] one found no significant difference, one had no fatal bleeding events. One study each found no significant difference in bleeding leading to reoperation or surgical site bleeding. Three RCTs found no significant difference in 30-day mortality (range of ORs 0.14 [95% CI 0.01 to 2.75] to 3.03 [95% CI 0.12 to 74.5]).[49-51]

Adherence

No study reported on adherence.

Key Question 1 (THR): LMWH Versus FXaI

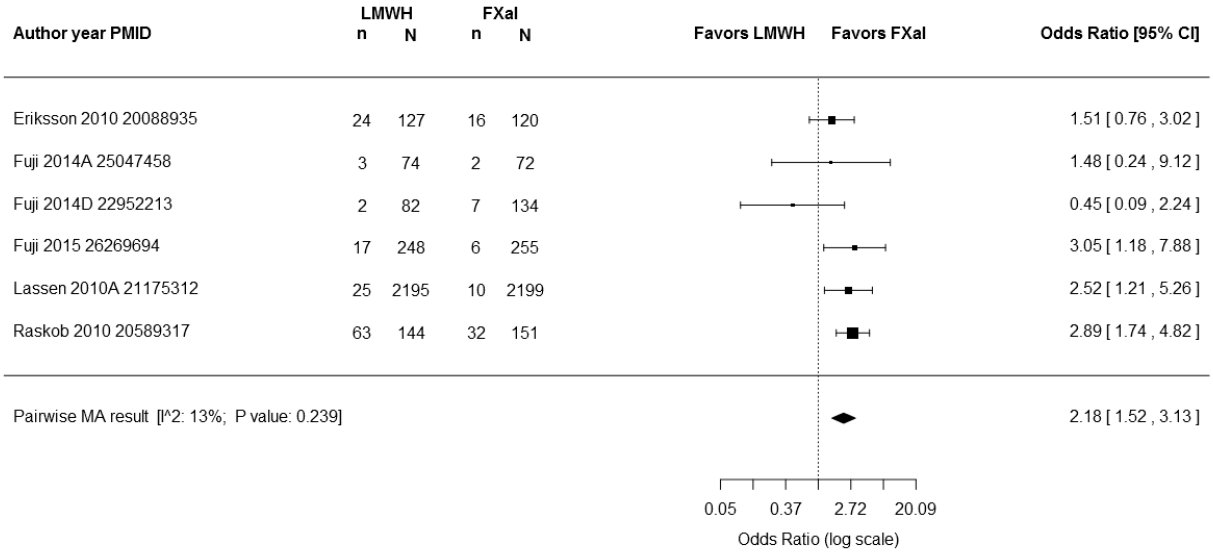
Eleven RCTs (N=12,472) compared LMWH versus FXaI;[24, 26, 54-62] one NRCS also evaluated this comparison.[27] All 12 studies reported on VTE-related outcomes.

Total VTE

Six RCTs (N=5801) compared LMWH and FXaI and reported the occurrence of total VTE with a wide range of event rates across studies (1.1 to 43.8% with LMWH, 0.5 to 21.2% with FXaI).[24, 26, 54-56, 58] No pattern or clear explanation could be found for differences in rates of VTE across studies. It is likely that studies differed in their definitions and methods for diagnosing VTE; however, they did not report sufficient data to explain the differences. Both the studies

with the lowest and highest rates of VTE used mandatory bilateral venography. The rate was significantly lower in the FXaI group in three RCTs.[24, 26, 54] Meta-analysis of the six RCTs yielded a summary OR of 2.18 (95% CI 1.52 to 3.13) for the risk of total VTE, significantly favoring FXaI. Studies were homogeneous (I^2 = 13%, P = 0.24) (Figure 4) even though specific drugs, doses, regimens, and risks of VTE varied across RCTs.

Figure 4. Forest plot: Total hip replacement, total venothromboembolism, LMWH versus FXaI

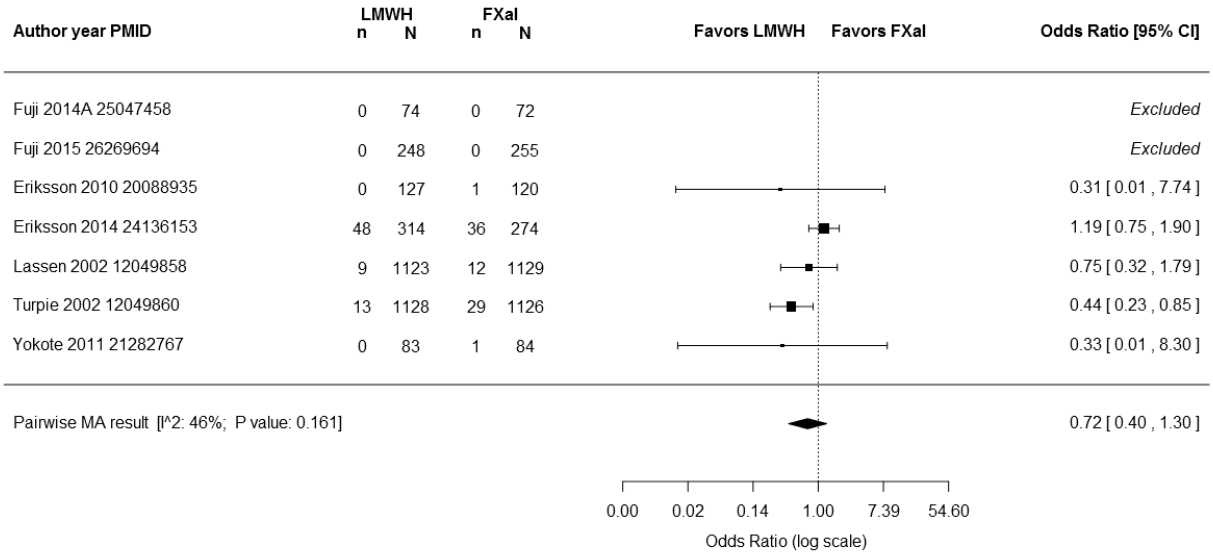


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic VTE

Seven RCTs (N=6157) reported on symptomatic VTE for comparisons of LMWH and FXaI (0% to 15.3% in LMWH, 0% to 13.1% in FXaI).[54, 56-58, 60-62] The rate was lower in the FXaI group in four RCTs,[58, 60-62] statistically significant so in one.[61] Two RCTs[54, 56] reported no occurrence of symptomatic VTE in either group. Meta-analysis of the other five RCTs yielded a summary OR of 0.72 (95% CI 0.40 to 1.30) for the risk of symptomatic VTE, significantly favoring FXaI. Study results were homogeneous (I^2 = 46%, P = 0.16) (Figure 5).

Figure 5. Forest plot: Total hip replacement, symptomatic venothromboembolism, LMWH versus FXaI

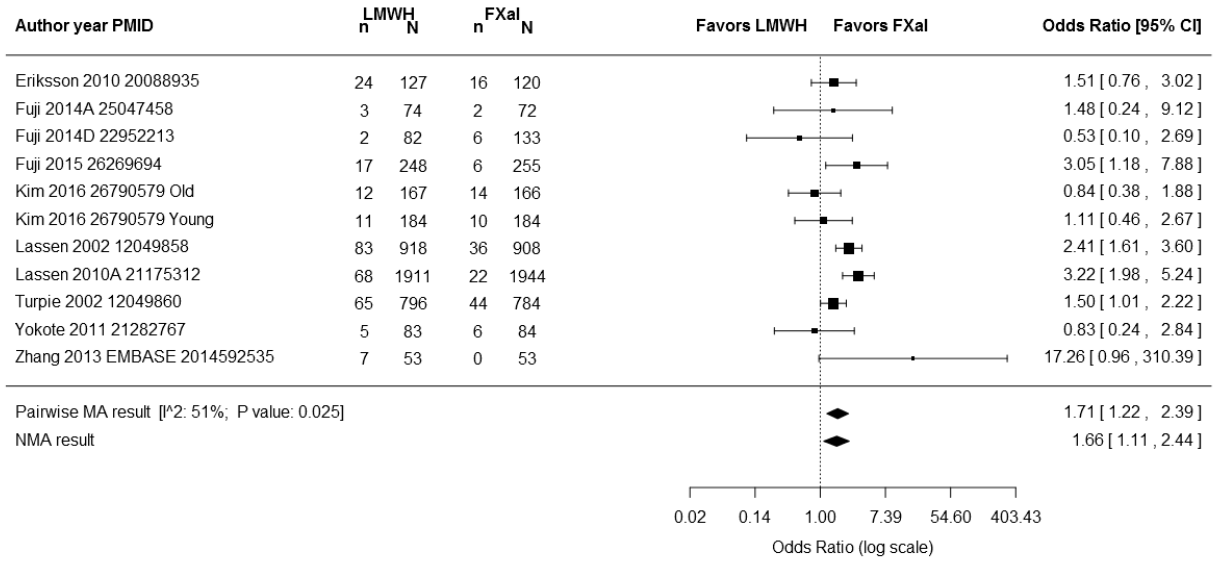


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Total DVT

Ten RCTs (N=9346) that compared LMWH and FXaI reported total DVT (2.4 to 18.9% in LMWH, 0% to 13.3% in FXaI).[24, 54-56, 58, 60-64] The rate was significantly lower in the FXaI group in four RCTs.[24, 54, 61, 62] Meta-analysis of the nine RCTs yielded a summary OR of 1.71 (95% CI 1.22 to 2.39) for the risk of total DVT, significantly favoring FXaI. There was significant heterogeneity across the RCTs (I^2 = 51%, P = 0.025) (Figure 6). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs. A single NRCS found no significant difference between intervention classes (Appendix Table F4).[27]

Figure 6. Forest plot: Total hip replacement, total deep vein thrombosis, LMWH versus FXaI

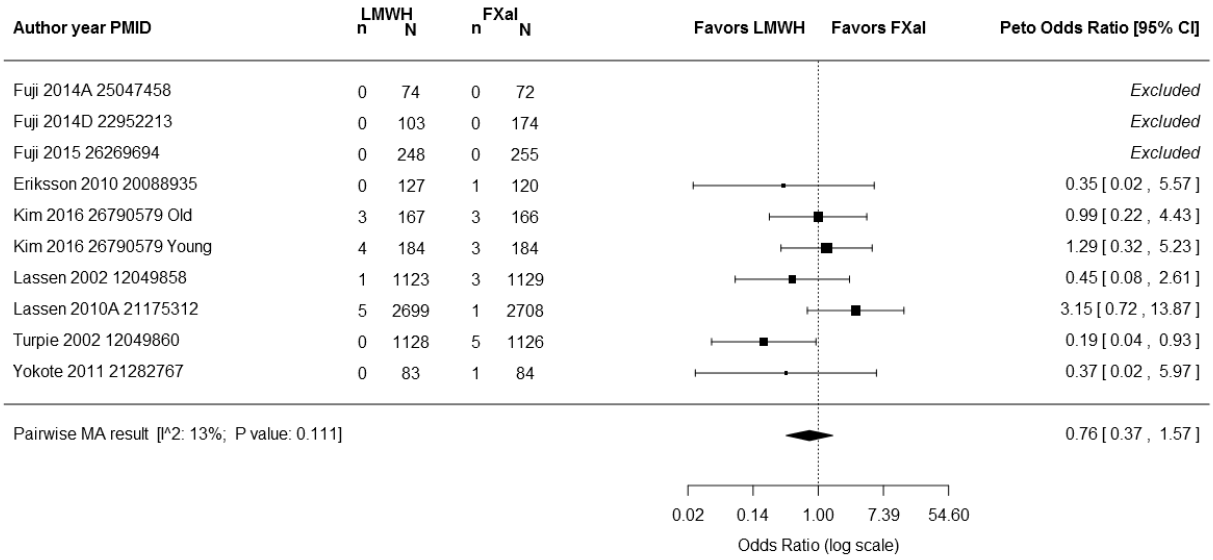


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic DVT

Nine RCTs (N=11,954) that assessed LMWH and FXaI reported symptomatic DVT (0% to 0.3% in LMWH, 0% to 1.2% in FXaI).[24, 54-56, 58, 60-63] Patients who received LMWH had a lower rate in four RCTs.[58, 60-62] Three RCTs[54-56] had no patients with symptomatic DVT in either study arm. Meta-analysis of the other six RCTs found an imprecise estimate of OR with no significant difference between the two drug classes for the risk of symptomatic DVT (summary OR=0.76; 95% CI 0.37 to 1.57). There was significant statistical heterogeneity across the RCTs (I^2 = 47%, P = 0.01) (Figure 7). Because of the relative rarity of the outcome (generally <1%), meta-analysis was conducted with Peto's fixed effect model; sensitivity analysis with the Mantel-Haenszel method yielded similar results. No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 7. Forest plot: Total hip replacement, symptomatic deep vein thrombosis, LMWH versus FXaI

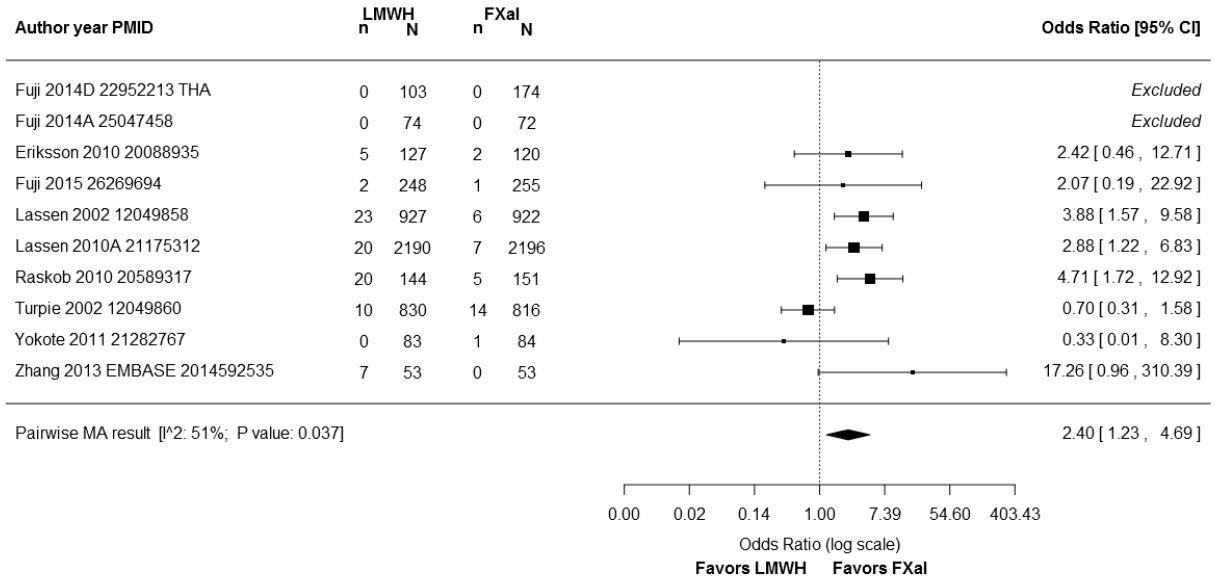


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effect model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Ten RCTs (N=9622) comparing LMWH and FXaI reported proximal DVT (0% to 13.9% in LMWH, 0% to 3.3% in FXaI).[24, 26, 54-56, 58, 60-62, 64] The rate was significantly lower in patients who received FXaI in three RCTs.[24, 26, 62] Two RCTs reported no proximal DVT in either comparison group.[55, 56] Meta-analysis of the other eight RCTs yielded a summary OR of 2.40 (95% CI 1.23 to 4.69), finding a significantly lower risk of proximal DVT in the FXaI group. Significant heterogeneity was shown across the RCTs (I^2 = 51%, P = 0.037) (Figure 8). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 8. Forest plot: Total hip replacement, proximal deep vein thrombosis, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other VTE Outcomes

Four RCTs[24, 60-62] and one NRCS[27] reported on total PE, but there were no PE events in one RCT and in the NRCS. Among the remaining three studies, no significant differences were found (range of ORs 0.33 [95% CI 0.11 to 1.03] to 1.67 [95% CI 0.40 to 7.01]).[b] Nine studies[24, 54, 56-58, 60-63] reported on fatal PEs, but only two studies had fatal PE events; the two studies found no significant differences (range of ORs 0.33 [95% CI 0.01 to 8.21] to 2.00 [95% CI 0.18 to 22.1]). Similarly, six studies reported on symptomatic PEs, of which only three studies had symptomatic PE events, finding no significant difference between intervention classes (range of ORs 0.33 to 0.99).

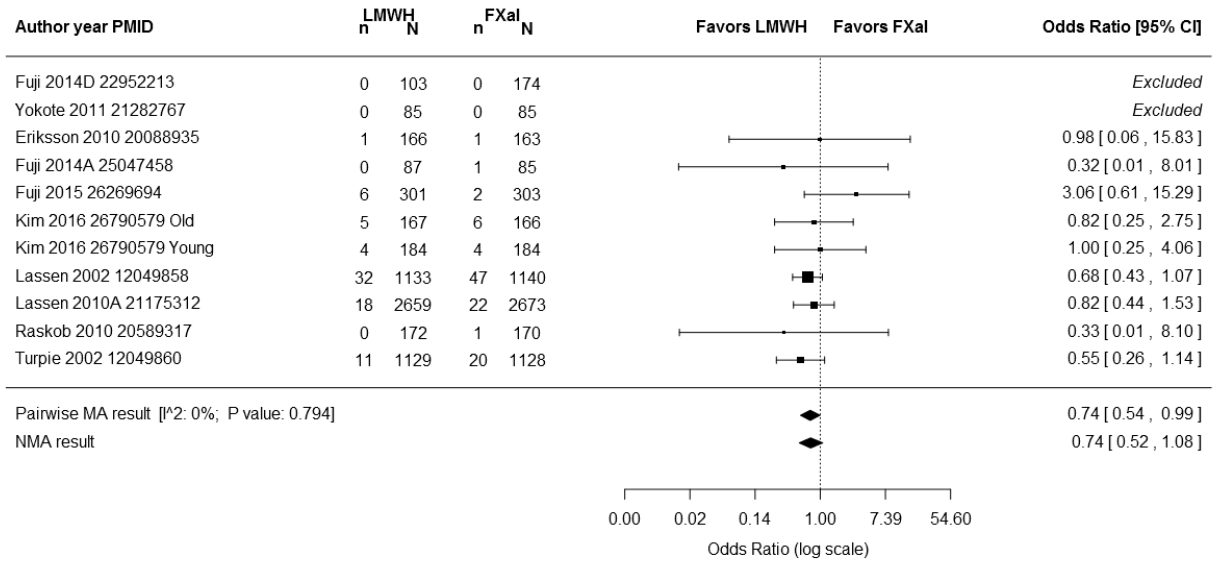
Major Bleeding

Ten RCTs (N=12,457) reported major bleeding for the comparison of LMWH and FXaI (0% to 3.0% in LMWH, 0% to 4.1% in FXaI).[24, 26, 54-56, 58, 60-63] The rate was lower in the LMWH group in seven RCTs.[24, 26, 56, 58, 61-63] Two RCTs[55, 60] reported no major bleeding in either comparison group. Meta-analysis of the remaining eight RCTs yielded a just-significant

[b] Since fewer than four RCTs had analyzable data, we did not meta-analyze the comparisons in this section, per protocol.

difference between the two classes for the risk of major bleeding (summary OR=0.74; 95% CI 0.54 to 0.99), favoring LMWH. Study results were homogeneous (I^2 = 0%, P = 0.79) (Figure 9).

Figure 9. Forest plot: Total hip replacement, major bleeding, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

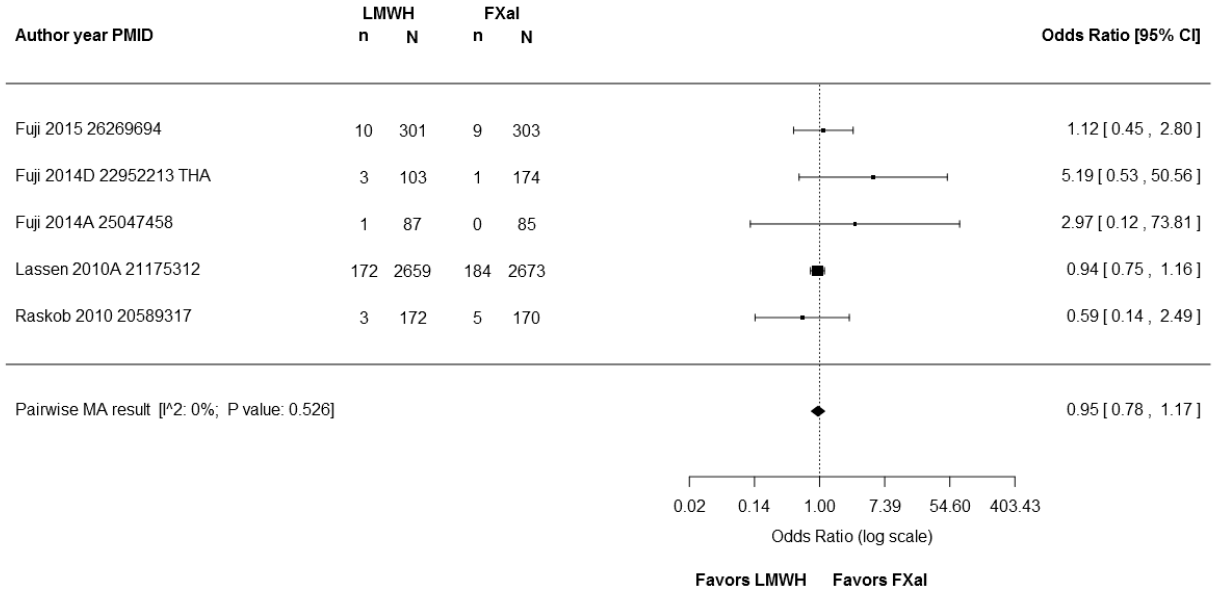
Other Bleeding Events

Three RCTs reported that no patients had fatal bleeding events.[24, 61, 62] The three RCTs reported no significant difference in bleeding leading to reoperation (range of ORs 0.60 [95% CI 0.14 to 2.53] to 1.01 [95% CI 0.06 to 16.1]).[24, 61, 62] Similarly, three studies reported no significant difference in surgical site bleeding (range of ORs 0.50 [95% CI 0.12 to 2.00] to 0.89 [95% CI 0.45 to 1.75]).

Serious Adverse Events (Study-Defined)

Five RCTs (N=6727) comparing LMWH versus FXaI reported serious adverse events (1.2 to 6.5% in LMWH, 0% to 6.9% in FXaI).[24, 26, 54, 55, 65] Two studies reported a lower rate in the LMWH group.[24, 26] No significant difference was shown in the meta-analysis of the five studies for the risk of serious adverse events between the two drug classes (summary OR=0.95, 95% CI 0.78 to 1.17). Study results were homogeneous (I^2 = 0%, P = 0.53) (Figure 10).

Figure 10. Forest plot: Total hip replacement, serious adverse events, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Five RCTs reported on 30-day mortality,[24, 55, 61-63] but two had no mortality events; the remaining three studies found no significant difference between intervention classes. One study reported no joint or wound infections.

Adherence

Two RCTs found conflicting results regarding adherence.[24, 56] One study found significantly better adherence with LMWH (OR 2.64, 95% CI 1.35 to 5.14); one study found no significant difference, nominally favoring FXaI (OR 0.11, 95% CI 0.01 to 2.05).

Key Question 1 (THR): LMWH Versus Mechanical Devices

Three RCTs (N=732) compared LMWH versus mechanical devices.[66-68] No significant differences were found for VTE outcomes. One RCT found no significant difference in total VTE. One RCT each found no significant differences in total PE or symptomatic PE. A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between mechanical devices and LMWH (OR 1.20, 95% CI 0.46 to 3.53), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F4).[29] Two RCTs had no fatal PEs. Three studies found no significant differences in total DVT (range of ORs 0.70 [95% CI 0.36 to 1.36] to 1.03 [95% CI 0.38 to 2.81]). The same three studies found no significant

differences in proximal DVTs (range of ORs 0.67 [95% CI 0.31 to 1.45] to 1.00 [95% CI 0.06 to 16.9]). Two studies reported on proximal DVTs; one had no proximal DVT events and the other found no significant difference in event rates.

One study found much more frequent major bleeding with LMWH than mechanical devices (11/194 vs. 0/198; OR 24.9, 95% CI 1.46 to 425),[67] but no significant difference in total serious adverse events. Another study had no fatal bleeding events or 30-day deaths.

No study reported on adherence.

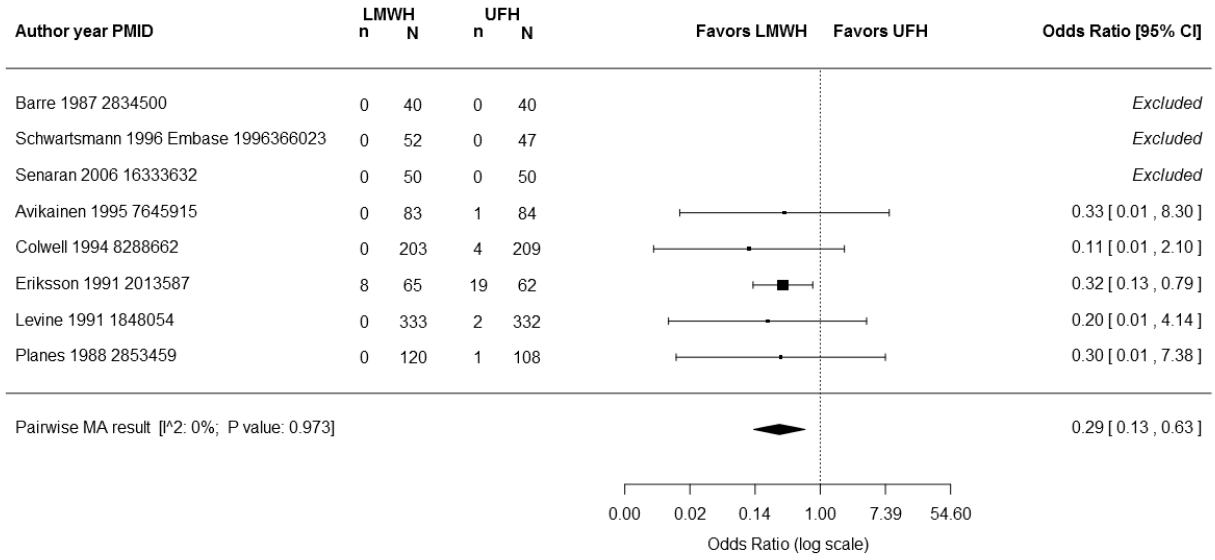
Key Question 1 (THR): LMWH Versus UFH

Ten RCTs (N=2387) reported on comparisons of LMWH versus UFH.[69-78] All 10 reported VTE-related outcomes.

Total PE

Eight RCTs (N=1878) that compared LMWH and UFH reported total PE (0% to 12.3% in LMWH, 0% to 30.6% in UFH).[69-71, 74-78] The rate was lower in the LMWH group in five RCTs,[69-71, 74, 78] which was statistically significant in one.[70] Three RCTs reported no occurrence of PE in either comparison group.[75-77] Meta-analysis of the remaining five RCTs yielded a summary OR of 0.29 (95% CI 0.13 to 0.63) for the risk of total PE, statistically significantly favoring LMWH. Study results were homogeneous (I^2 = 0%, P = 0.97) (Figure 11).

Figure 11. Forest plot: Total hip replacement, total pulmonary embolism, LMWH versus UFH

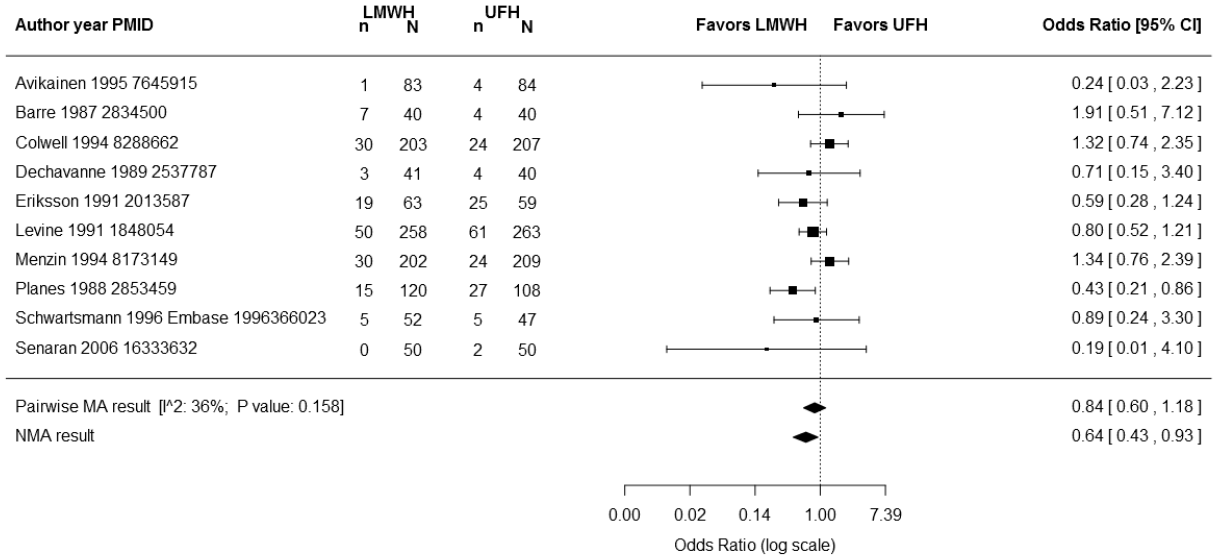


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Total DVT

Ten RCTs (N=2219) reported total DVT in comparisons of LMWH and UFH (0% to 30.2% in LMWH, 4.0% to 42.4% in UFH).[69-78] The rate was lower in the LMWH group in seven RCTs,[69-72, 76-78] which was statistically significant in one.[71] Meta-analysis of the 10 RCTs found no significant difference between the two drug classes for the risk of total DVT (summary OR=0.84; 95% CI 0.60 to 1.18). Study results were homogeneous (I^2 = 36%, P = 0.16) (Figure 12).

Figure 12. Forest plot: Total hip replacement, total deep vein thrombosis, LMWH versus UFH

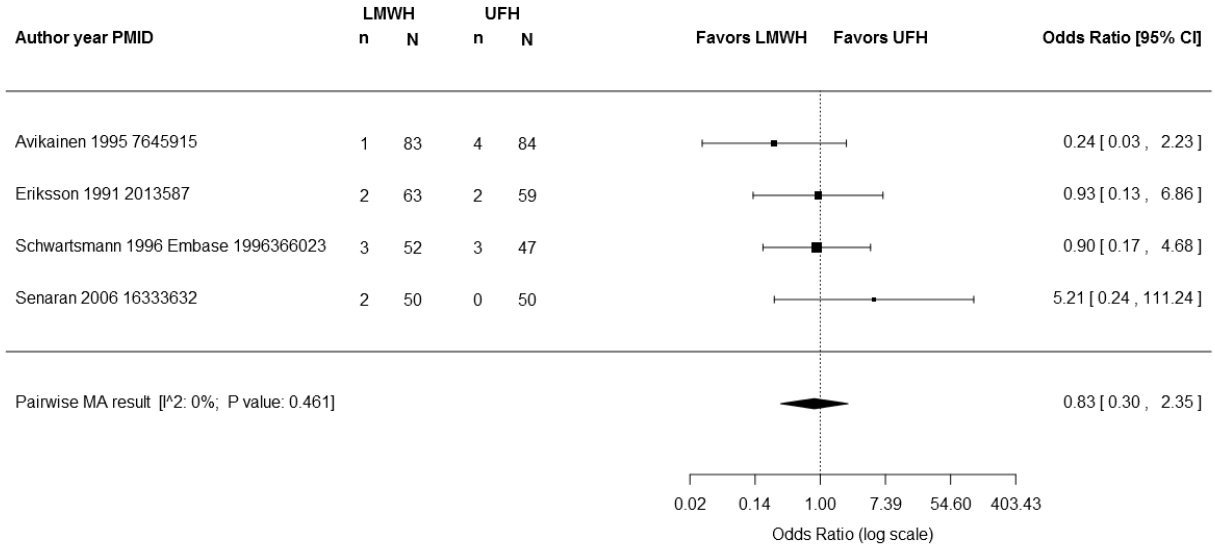


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Symptomatic DVT

Four RCTs (N=488) reported on symptomatic DVT comparing LMWH and UFH (1.2 to 5.8% in LMWH, 0% to 6.4% in UFH).[70, 76-78] Patients who received LMWH had a lower event rate in three RCTs. Meta-analysis of the four RCTs found an imprecise estimate of OR with no significant difference for the risk of symptomatic DVT between the two comparison groups (summary OR=0.83, 95% CI 0.30 to 2.35). Study results were homogeneous (I^2 = 0%, P = 0.46) (Figure 13).

Figure 13. Forest plot: Total hip replacement, symptomatic deep vein thrombosis, LMWH versus UFH

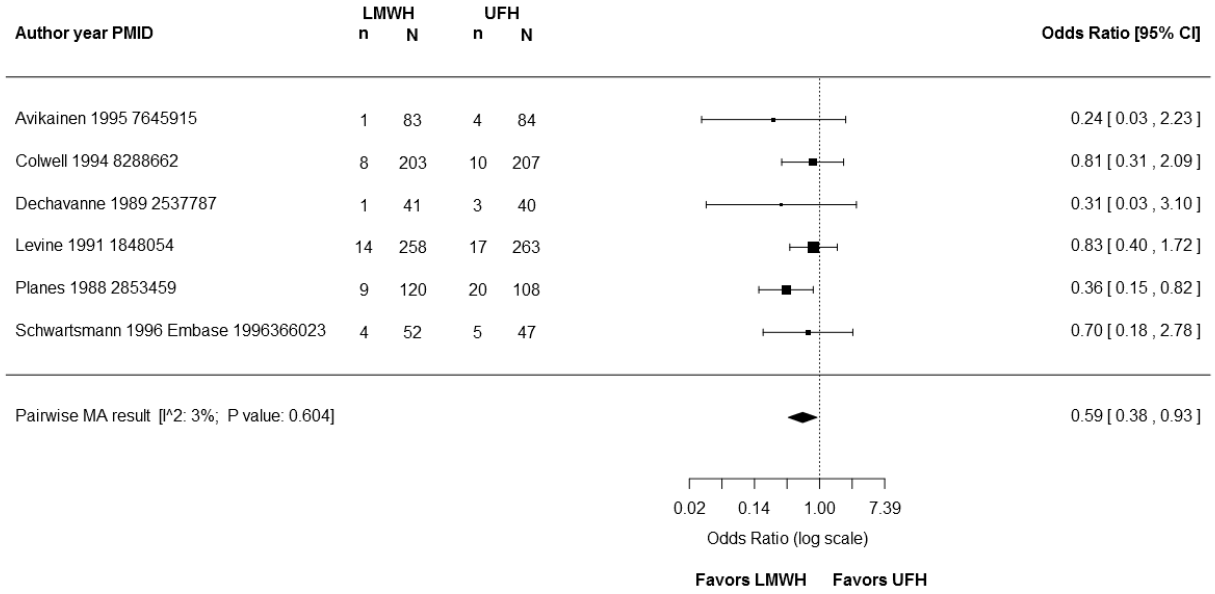


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Proximal DVT

Six RCTs (N=1506) compared LMWH and UFH and reported proximal DVT (1.2 to 7.7% in LMWH, 4.8 to 18.5% in UFH).[69, 71, 72, 74, 77, 78] The event rate was significantly lower in the LMWH group in one RCT.[71] Meta-analysis of the six RCTs yielded a summary OR of 0.59 (95% CI 0.38 to 0.93) for the risk of proximal DVT, significantly favoring LMWH. Study results were homogeneous (I^2 = 3%, P = 0.60) (Figure 14).

Figure 14. Forest plot: Total hip replacement, proximal deep vein thrombosis, LMWH versus UFH



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

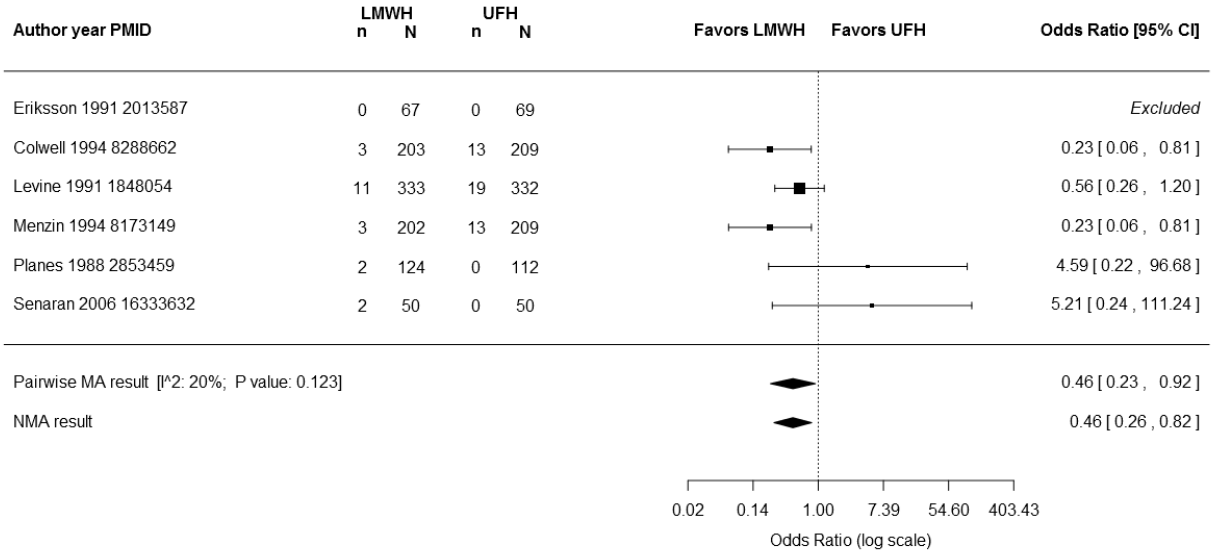
Other VTE Outcomes

One RCT found no significant difference in symptomatic VTE.[76] Seven studies reported no fatal PE events.[69-71, 74-77]

Major Bleeding

Six RCTs (N=1960) that examined LMWH and UFH reported major bleeding (0% to 4.0% in LMWH, 0% to 6.2% in UFH).[69-71, 73, 74, 76] The rate was lower in patients who received LMWH in three RCTs,[69, 73, 74] statistically significantly so in two.[73, 74] One RCT reported no major bleeding in either group. Meta-analysis of the other five RCTs yielded a summary OR of 0.46 (95% CI 0.23 to 0.92) for the risk of major bleeding, significantly favoring LMWH. Study results were homogeneous (I^2 = 20%, P = 0.12) (Figure 15).

Figure 15. Forest plot: Total hip replacement, major bleeding, LMWH versus UFH



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, UFH = unfractionated heparin.

Other Bleeding Events

Six RCTs had no fatal bleeding events,[69-71, 75-77] one of which also reported no bleeding events leading to reoperation. Two studies found no significant differences in rates of surgical site bleeding. Six studies reported on 30-day mortality but four of the studies had no deaths[c] and the remaining two found no significant differences in mortality rates.[69-71, 74, 76, 77]

Other Adverse Events

Three RCTs found no significant differences in rates of heparin-induced thrombocytopenia, but one of the studies had no events.[69, 74, 76]

Adherence

No study reported on adherence.

Key Question 1 (THR): LMWH Versus VKA

Four RCTs (N=5332) compared LMWH and VKA.[79-82] All reported on VTE-related outcomes.

[c] Since fewer than four RCTs had analyzable data, we did not meta-analyze this comparison, per protocol.

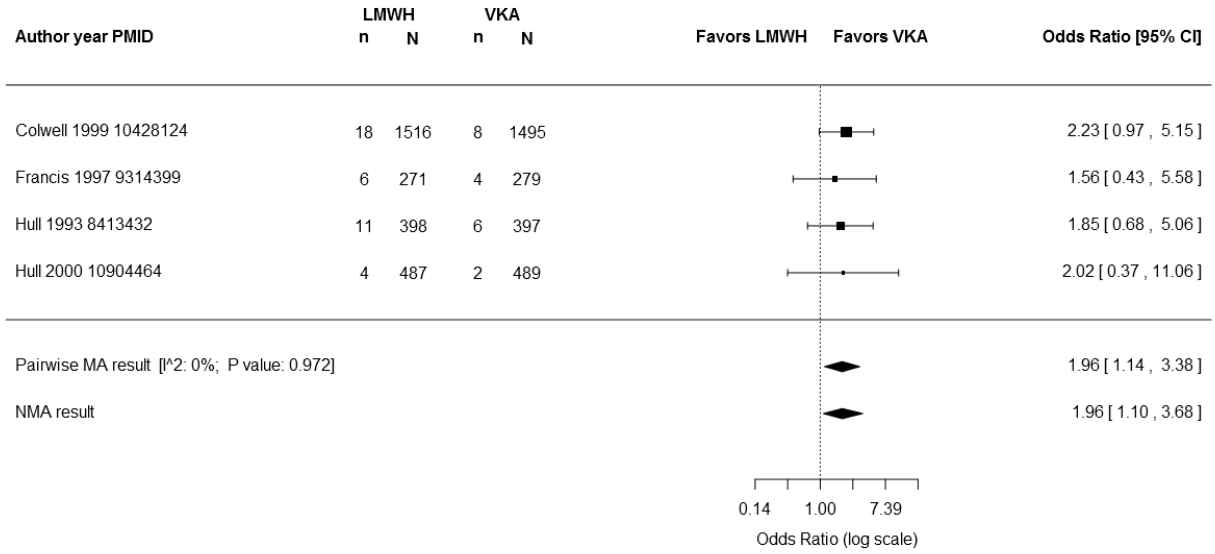
VTE Outcomes

Two RCTs found no significant difference in symptomatic VTE.[79, 80] Three RCTs found no significant differences in total PE (with no events in one study) and in fatal PE (with no events in two studies).[79-81] The three studies found no significant differences in total DVTs, two of which also found no significant differences in symptomatic DVTs.[79-81] However, one of the three studies found significantly fewer proximal DVTs with LMWH than VKA, but the three studies were not consistent (range of ORs 0.27 [95% CI 0.07 to 0.98] to 1.27 [95% CI 0.60 to 2.69]).

Major Bleeding

Four RCTs (N=5332) reported major bleeding which assessed LMWH and VKA (0.8 to 2.8% in LMWH, 0.4 to 1.5% in VKA).[79-82] The rate was lower in the VKA group in all the RCTs. Meta-analysis of the four RCTs showed a significantly lower risk of major bleeding in the VKA group (summary OR=1.96, 95% CI 1.14 to 3.38). Study results were homogeneous (I^2 = 0%, P = 0.97) (Figure 16).

Figure 16. Forest plot: Total hip replacement, major bleeding, LMWH versus VKA



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Other Bleeding

Two RCTs reported no fatal bleeding events.[80, 81] One study found no significant difference in bleeding events leading to reoperation.[82] Two of three studies found significant differences in surgical site bleeding, with all three studies favoring VKA (range of ORs 1.63 [95% CI 0.88 to

3.03] to 4.26 [95% CI 1.19 to 15.3]).[79, 81, 82] One study reported no 30-day mortality events and one study reported no incidents of heparin-induced thrombocytopenia.[81]

Adherence

No study reported on adherence.

Key Question 1 (THR): Mechanical Device Versus UFH

One RCT (N=132) compared a mechanical device and UFH.[83] The study found significantly fewer total DVTs with the mechanical device, no fatal bleeding events, and no significant difference in 30-day mortality.

Key Question 1 (THR): Mechanical Devices Versus VKA

Three RCTs (N=434) compared a mechanical device with VKA.[84-86] One study reported no PE events in either arm. A U.S.-based registry NRCS of 14,657 THR patients found no significant difference in total PE between mechanical devices and LMWH (OR 1.34, 95% CI 0.51 to 3.53), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F4).[29] One of three RCTs found a statistically significant difference in total DVTs favoring mechanical devices, but the other two RCTs found no significant difference; the range of OR estimates was 0.18 (95% CI 0.05 to 0.67) to 1.00 (95% CI 0.41 to 2.45). However, the same three RCTs consistently found more proximal DVTs mechanical devices than VKA, but again only one study was statistically significant; the range of OR estimates was 2.39 (95% CI 0.77 to 7.41) to 4.69 (95% CI 0.22 to 100.4).

No bleeding events were found for major bleeding (1 RCT), fatal bleeding (2 RCTs), or bleeding leading to reoperation (1 RCT). Two RCTs reported on 30-day mortality; one had no deaths and one found no significant difference between intervention classes.

Table 1. Results summary: Total hip replacement, intervention class versus class comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
Antiplatelet vs. VKA	DVT, Total	1	0.71 (0.34, 1.47)			
	DVT, Proximal	1	0.31 (0.08, 1.18)			
Antiplatelet vs. VKA (+mechanical device both arms)	PE, Total	1	3.00 (0.12, 74.9)			
	DVT, Proximal	1	1.13 (0.36, 3.55)			
DTI vs. FXaI (+LMWH both arms)	DVT, Total	1	0.54 (0.12, 2.42)			
DTI vs. UFH	PE, Total	2	0.11 (0.01, 2.03)	3.42 (0.14, 84.4)		
	PE, Fatal	2	No estimate			2 RCTs
	DVT, Total	2	**0.26** (**0.13, 0.50**)	**0.44** (**0.28, 0.69**)		
	DVT, Proximal	2	**0.13** (**0.05, 0.31**)	**0.18** (**0.05, 0.62**)		
	Bleeding, Fatal	2				2 RCTs
	Bleeding, Leading to reoperation	2	2.01 (0.37, 11.1)			1 RCT
	Bleeding, Surgical site/joint	1	1.15 (0.41, 3.21)			
	Mortality, 30 day or in-hospital	2	0.20 (0.01, 4.15)	0.38 (0.02, 9.28)		
FEI vs. FXaI	VTE, Total	1	1.11 (0.44, 2.78)			
	VTE, Symptomatic	1	No estimate			1 RCT
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	1.11 (0.44, 2.78)			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	4.02 (0.45, 36.3)			
	Bleeding, Major	1	11.22 (0.62, 204)			
	Bleeding, Surgical site/joint	1	**2.87** (**1.30, 6.34**)			
	Mortality, 30 day or in-hospital	1	0.33 (0.01, 8.15)			
LMWH vs. antiplatelet	PE, total	2	0.94 (0.75, 1.17)	0.2% vs. 1.7%		
	DVT, symptomatic	1	0.84 (0.70, 1.03)			
	Bleeding, major	1	0.95 (0.77, 1.17)			
LMWH vs. DTI	VTE, Symptomatic	1	6.09 (0.73, 50.6)			
	PE, Total	2	0.60 (0.14, 2.50)	2.40 (0.62, 9.30)		
	PE, Fatal	2	0.34 (0.01, 8.36)			1 RCT
	DVT, Total	3	1.14 (0.79, 1.64)	1.18 (0.67, 2.07)	**1.52** (**1.19, 1.94**)	

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	DVT, Symptomatic	2	0.17 (0.02, 1.37)	9.12 (0.49, 170)		
	DVT, Proximal	3	1.35 (0.53, 3.42)	**1.73** (**1.13, 2.65**)	**1.89** (**1.04, 3.44**)	
	Bleeding, Major	*4 (MA)*	*0.79 (0.55, 1.14)*			
	Bleeding, Fatal	2	0.33 (0.01, 8.13)			1 RCT
	Bleeding, Leading to reoperation	1	1.49 (0.25, 8.94)			
	Bleeding, Surgical site/joint	1	1.03 (0.86, 1.24)			
	Mortality, 30 day or in-hospital	3	0.14 (0.01, 2.75)	0.25 (0.03, 2.28)	3.03 (0.12, 74.5)	
LMWH vs. FXaI	*VTE, Total*	*6 (MA)*	***2.18 (1.52, 3.13)***			
	VTE, Symptomatic	*7 (MA)*	***0.72 (0.40, 1.30)***			2 RCTs
	PE, Total	4	0.33 (0.11, 1.03)	1.01 (0.14, 7.15)	1.67 (0.40, 7.01)	1 RCT
	PE, Fatal	9	0.33 (0.01, 8.21)	2.00 (0.18, 22.1)		7 RCTs
	PE, Symptomatic	6	0.33 (0.01, 8.19)	0.56 (0.02, 13.8)	0.99 (0.06, 16.0)	3 RCTs
	DVT, Total	*10 (MA)*	***1.71 (1.22, 2.39)***			
	DVT, Symptomatic	*9 (MA)*	*0.76 (0.37, 1.57)*			3 RCTs
	DVT, Proximal	*10 (MA)*	***2.40 (1.23, 4.69)***			2 RCTs
	Bleeding, Major	*10 (MA)*	***0.74 (0.54, 0.99)***			2 RCTs
	Bleeding, Fatal	*3*	No estimate			3 RCTs
	Bleeding, Leading to reoperation	3	0.60 (0.14, 2.53)	1.00 (0.14, 7.11)	1.01 (0.06, 16.1)	
	Bleeding, Surgical site/joint	3	0.50 (0.05, 5.56)	0.72 (0.44, 1.17)	0.89 (0.45, 1.75)	
	Mortality, 30 day or in-hospital	5	0.50 (0.12, 2.00)	0.50 (0.12, 2.00)	2.02 (0.37, 11.0)	2 RCT
	Infection, Joint	1	No estimate			1 RCT
	Infection, Wound	1	No estimate			1 RCT
	Adverse event, Serious	*5 (MA)*	*0.95 (0.78, 1.17)*			
	Adherent/Compliant	2	0.11 (0.01, 2.05)	**2.64** (**1.35, 5.14**)		
LMWH vs. Mechanical Devices	VTE, Total	1	1.03 (0.42, 2.54)			
	PE, Total	1	0.33 (0.01, 8.08)			
	PE, Fatal	2	No estimate			2 RCTs
	PE, Symptomatic	1	1.03 (0.14, 7.40)			
	DVT, Total	3	0.70 (0.36, 1.36)	1.00 (0.06, 17.0)	1.03 (0.38, 2.81)	
	DVT, Symptomatic	2	2.98 (0.12, 73.8)			1 RCT
	DVT, Proximal	3	0.67 (0.31, 1.45)	0.68 (0.11, 4.14)	1.00 (0.06, 16.9)	
	Bleeding, Major	1	**24.9** (**1.46, 425**)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	Adverse event, Serious	1	3.53 (0.96, 13.0)			
LMWH vs. UFH	VTE, Symptomatic	1	1.00 (0.14, 7.39)			
	PE, Total	*8 (MA)*	***0.29 (0.13, 0.63)***			3 RCTs
	PE, Fatal	7	No estimate			7 RCTs
	DVT, Total	*10 (MA)*	*0.84 (0.60, 1.18)*			
	DVT, Symptomatic	*4 (MA)*	*0.83 (0.30, 2.35)*			
	DVT, Proximal	*6 (MA)*	***0.59 (0.38, 0.93)***			
	Bleeding, Major	*6 (MA)*	***0.46 (0.23, 0.92)***			1 RCT
	Bleeding, Fatal	6	No estimate			6 RCTs
	Bleeding, Leading to reoperation	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	2	0.14 (0.02, 1.17)	0.73 (0.16, 3.46)		
	Mortality, 30 day or in-hospital	6	0.20 (0.01, 4.27)	0.34 (0.01, 8.45)		4 RCTs
	Heparin-induced thrombocytopenia	3	0.05 (<0.01, 0.88)	0.34 (0.01, 8.43)		1 RCT
LMWH vs. VKA	VTE, Symptomatic	2	0.97 (0.66, 1.41)	3.02 (0.61, 15.1)		
	PE, Total	3	1.24 (0.58, 2.65)	3.00 (0.12, 73.9)		1 RCT
	PE, Fatal	3	2.96 (0.12, 72.7)			2 RCTs
	DVT, Total	3	**0.48** (**0.32, 0.72**)	**0.49** (**0.29, 0.82**)	0.87 (0.60, 1.25)	
	DVT, Symptomatic	2	0.66 (0.29, 1.49)	1.03 (0.69, 1.55)		
	DVT, Proximal	3	**0.27** (**0.07, 0.98**)	0.60 (0.26, 1.35)	1.27 (0.60, 2.69)	
	Bleeding, Major	*4 (MA)*	***1.96 (1.10, 3.38)***			
	Bleeding, Fatal	2	No estimate			2 RCTs
	Bleeding, Leading to reoperation	1	3.10 (0.13, 76.4)			
	Bleeding, Surgical site/joint	3	1.63 (0.88, 3.03)	**2.78** (**1.00, 7.73**)	**4.26** (**1.19, 15.3**)	
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
	Heparin-induced thrombocytopenia	1	No estimate			1 RCT
Mechanical Devices vs. UFH	DVT, Total	1	**0.28** (**0.12, 0.67**)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.32 (0.01, 7.96)			
Mechanical Devices vs. VKA	PE, Total	1	No estimate			1 RCT
	DVT, Total	3	**0.18** (**0.05, 0.67**)	0.80 (0.43, 1.48)	1.00 (0.41, 2.45)	
	DVT, Proximal	3	2.39 (0.77, 7.41)	**4.65** (**1.27, 17.0**)	4.69 (0.22, 100)	
	Bleeding, Major	1	No estimate			1 RCT
	Bleeding, Fatal	2	No estimate			2 RCTs

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	Bleeding, Leading to reoperation	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	2	1.05 (0.06, 17.1)			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, VKA = vitamin K antagonist, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, FEI = factor VIII inhibitor, UFH = unfractionated heparin.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Antiplatelet vs. VKA, OR = 0.71 favors antiplatelet).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Cross-Study Subgroup Analyses

As noted at the start of the *Results* section, studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithrombotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregression no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregression. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Key Question 1: Total Knee Replacement

The results summary table (Table 2) includes results for all reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 1 (TKR): Antiplatelet Drug Versus FXaI

One RCT (N=212) compared an antiplatelet drug versus an FXaI.[87] The study had no PE events, but found significantly fewer total DVT in the FXaI group and no significant difference in symptomatic DVT.

The study found no significant difference in wound complications between the two groups. The study did not report on adherence.

Key Question 1 (TKR): Antiplatelet Drug Versus Mechanical Devices

One RCT (N=119) compared an antiplatelet drug versus a mechanical device.[88] The study reported a significantly fewer total DVT in patients who received mechanical prophylaxis, but no significant difference in proximal DVT between the two classes. The study did not report adverse events or adherence data.

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between aspirin and mechanical devices (OR 0.63, 95% CI 0.32 to 1.26), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F5).[35]

Subgroup Analysis

The RCT compared subgroups of patients who received unilateral or bilateral TKR surgery. They found that in the unilateral surgery group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral surgery group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20).[88] Whether the treatment effect differed between unilateral and bilateral surgery subgroups was not analyzed.

Key Question 1 (TKR): Antiplatelet Drug Versus VKA

One RCT (N=189) comparing an antiplatelet drug versus a VKA found no significant difference in either total DVT or proximal DVT between the two classes.[43] The study did not report adverse events or adherence data.

Key Question 1 (TKR): DTI Versus FXaI

One RCT (N=80) compared DTI versus FXaI.[89] The study reported no total PE, no total DVT, and no major bleeding in either group. The study did not report adherence data.

Key Question 1 (TKR): LMWH Versus Antiplatelet Drug

Two RCTs (N=497) compared LMWH versus an antiplatelet drug.[87, 90] One study reported no total PEs in either group. It found no significant difference in total DVT and symptomatic DVT between the intervention classes. The study also found no significant difference in wound complications. The other study also found no significant differences between the two classes in total PE, total DVT, and proximal DVT. The study reported adherence of over 90 percent in both groups.

Key Question 1 (TKR): LMWH Versus DTI

Five RCTs (N=3514) compared LMWH versus DTI.[52, 89, 91-93] All reported on VTE-related outcomes.

VTE Outcomes

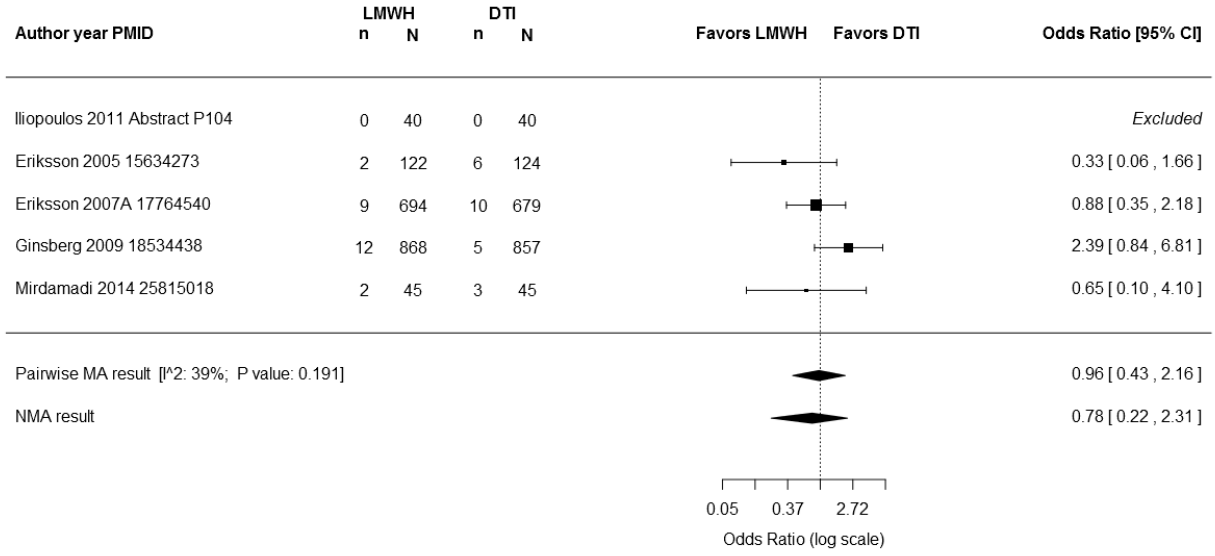
Two RCTs reported total PE;[89, 91] one had no PE events and the other found no significant difference between the two comparison groups. One study found no significant difference in fatal PE between arms, and one reported no fatal PE in either arm.[91, 93] Two studies reported total DVT;[52, 89] one had no DVT events but the other found significantly fewer total DVTs in the DTI group. Three RCTs found no significant differences in symptomatic DVT between the two drug classes with inconsistent estimates across studies, but one near-significant OR favoring DTI

(range of ORs 0.67 [95% CI 0.21 to 2.12] to 7.96 [95% CI 0.99 to 63.9]).[91-93] Two RCTs found no significant difference in proximal DVT between arms.[52, 92]

Major Bleeding

Five RCTs (N=3514) that compared LMWH and DTI reported major bleeding (0% to 4.4% in LMWH, 0% to 6.7% in DTI).[52, 89, 91-93] The rate was lower in the LMWH group in three RCTs.[52, 91, 93] One RCT reported no occurrence of major bleeding in either of the groups. Meta-analysis of the other four RCTs found an imprecise estimate of OR with no significant difference between the two drug classes for the risk of major bleeding (summary OR=0.96; 95% CI 0.43 to 2.16). Study results were homogeneous (I^2 = 39%, P = 0.19) (Figure 17).

Figure 17. Forest plot: Total knee replacement, major bleeding, LMWH versus DTI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Two RCTs reported no fatal bleeding.[91, 92] One study found no significant difference in bleeding leading to reoperation between the two classes.[91] One study reported significantly lower rate of bleeding at surgical site or joint in the DTI group.[92] One study found no significant difference in 30-day mortality.[91]

Adherence

No studies reported adherence data.

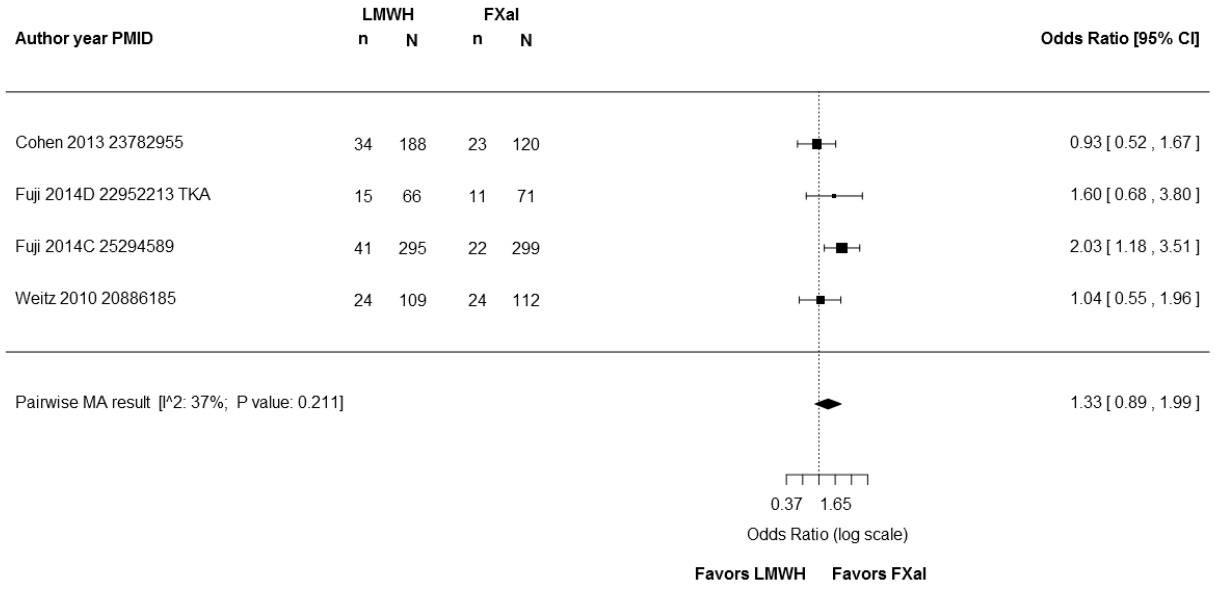
Key Question 1 (TKR): LMWH Versus FXaI

Ten RCTs (N=6350) compared LMWH versus FXaI.[55, 87, 89, 94-100] All 10 reported VTE-related outcomes.

Total VTE

Four RCTs[55, 98-100] (N=1260) reported the outcome of total VTE for the comparison of LMWH and FXaI (13.9% to 22.7% in LMWH, 7.4 to 21.4% in FXaI). Three RCTs[55, 98, 99] had a lower event rate in the FXaI group, which was statistically significant in one.[98] No significant difference was shown for the risk of total VTE between the two drug classes in the meta-analysis of the four RCTs (summary OR=1.33, 95% CI 0.89 to 1.99). Study results were homogeneous (I^2 = 37%, P = 0.21) (Figure 18).

Figure 18. Forest plot: Total knee replacement, total venothromboembolism, LMWH versus FXaI

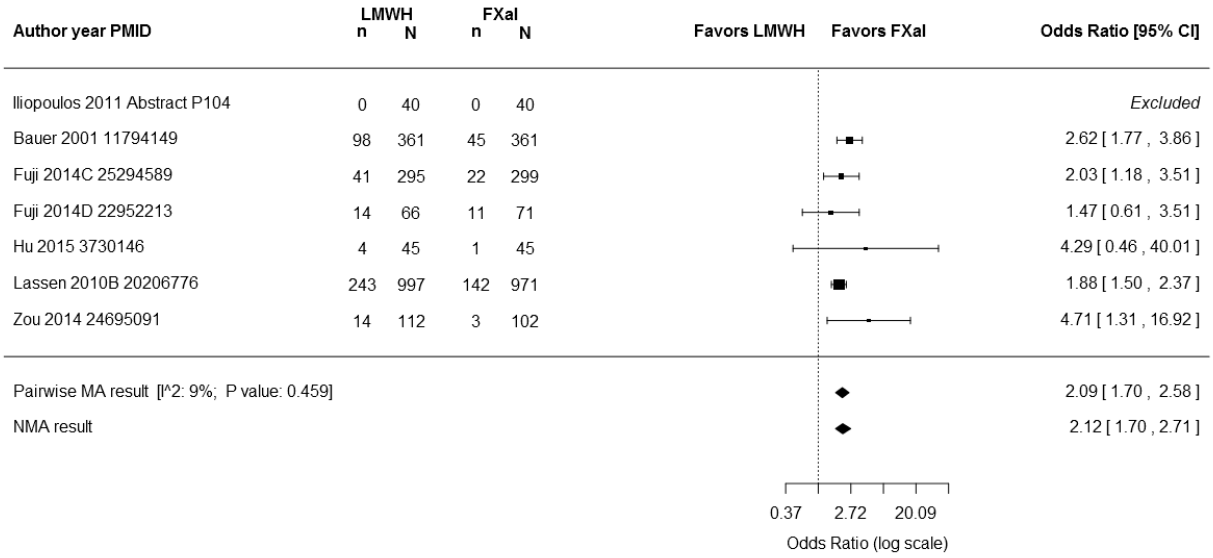


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Total DVT

Seven RCTs (N=3805) reported total DVT for comparisons of LMWH and FXaI (0% to 27.2% in LMWH, 0% to 15.5% in FXaI).[55, 87, 89, 95-98] The DVT rate was lower in the FXaI group in six RCTs,[55, 87, 95-98] statistically significantly so in four.[87, 96-98] One RCT reported no occurrence of DVT events in either comparison group.[89] Meta-analysis of the other six RCTs yielded a summary OR of 2.09 (95% CI 1.70 to 2.58) for the risk of total DVT, significantly favoring FXaI. Study results were homogeneous (I^2 = 9%, P = 0.46) (Figure 19).

Figure 19. Forest plot: Total knee replacement, total deep vein thrombosis, LMWH versus FXaI

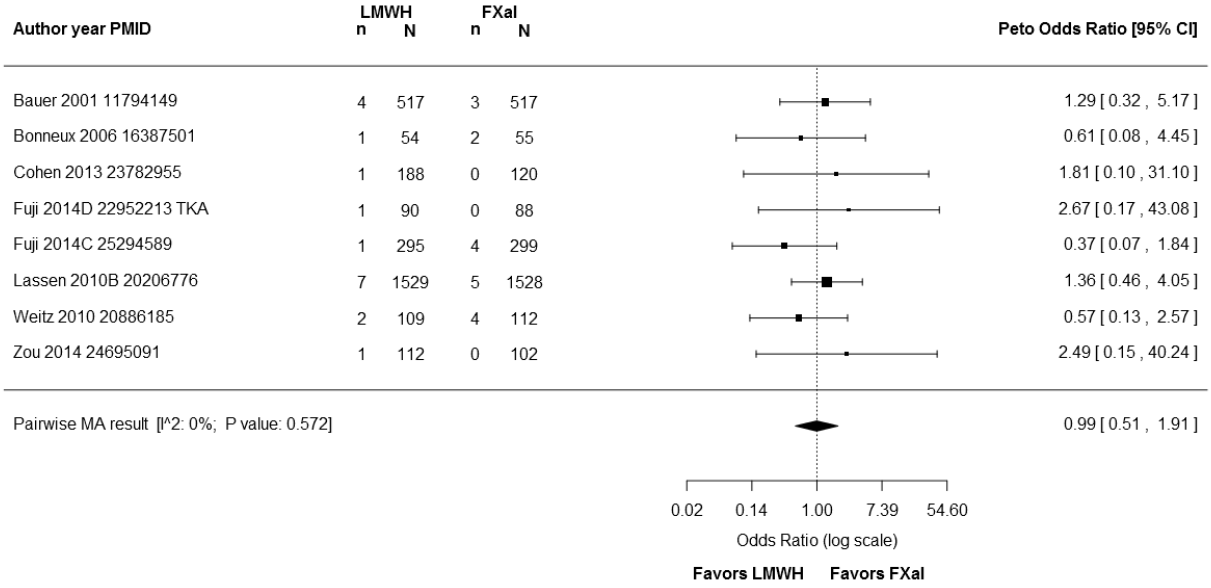


Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Symptomatic DVT

Eight RCTs (N=5715) comparing LMWH and FXaI reported symptomatic DVT (0.3 to 1.9% in LMWH, 0% to 3.6% in FXaI).[55, 87, 94, 96-100] The DVT rate was somewhat lower in the FXaI group in five RCTs.[55, 87, 96, 97, 100] Meta-analysis of the eight RCTs showed no significant difference between the two drug classes for the risk of symptomatic DVT (summary OR=0.99; 95% CI 0.51 to 1.91). Study results were homogeneous (I^2 = 0%, P = 0.57) (Figure 20). Because of the relative rarity of the outcome (generally <1%), meta-analysis was conducted with Peto's fixed effect model; sensitivity analysis with the Mantel-Haenszel method yielded similar results.

Figure 20. Forest plot: Total knee replacement, symptomatic deep vein thrombosis, LMWH versus FXaI

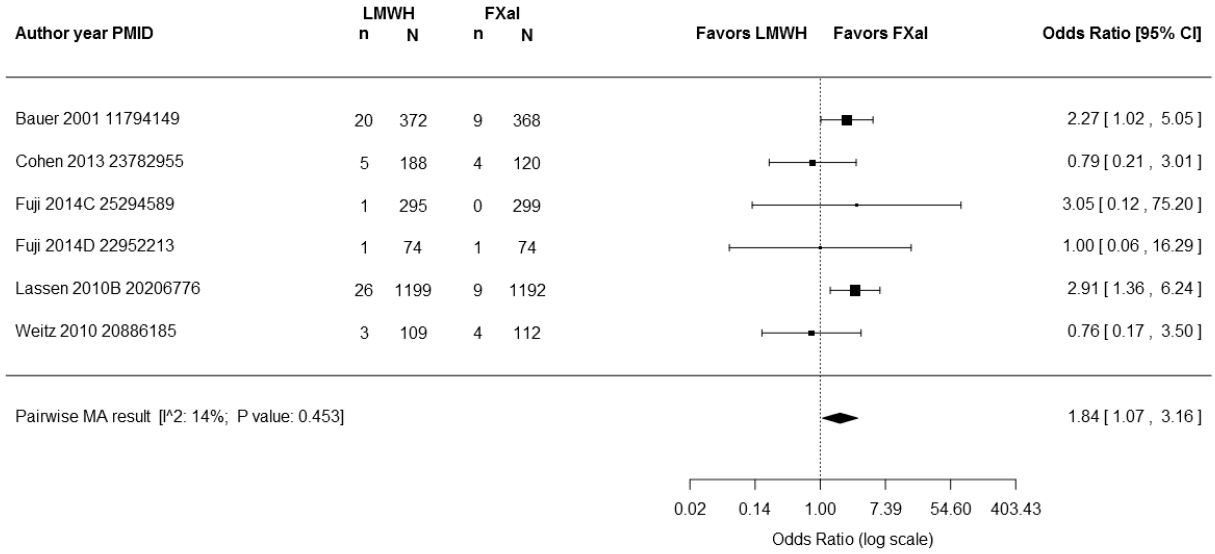


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effect model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Proximal DVT

Six RCTs (N=4402) reported proximal DVT for the comparison of LMWH and FXaI (0.3 to 5.4% in LMWH, 0% to 3.6% in FXaI).[55, 96-100] The rate was lower in the FXaI group in three RCTs;[96-98] statistically significant in two.[96, 97] Overall, the difference for the risk of proximal DVT was statistically significant between the two groups in the meta-analysis of the six RCTs (summary OR=1.84, 95% CI 1.07 to 3.16), favoring FXaI. Study results were homogeneous (I^2 = 14%, P = 0.45) (Figure 21).

Figure 21. Forest plot: Total knee replacement, proximal deep vein thrombosis, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other VTE Outcomes

Three RCTs found no significant difference in symptomatic VTE between the two classes (range of ORs 0.25 [95% CI 0.03 to 2.26] to 2.02 [95% CI 0.69 to 5.95])[d,97-99] Five RCTs reported total PE, but two had no PE events; the remaining three found no significant difference (range of ORs 0.14 [95% CI 0.02 to 1.16] to 2.59 [95% CI 0.29 to 23.4]).[87, 89, 96, 97, 100] Five RCTs reported fatal PE, but three had no fatal PE events; the two remaining found no significant difference.[96-100] Three RCTs reported on symptomatic PE, one with no symptomatic PE events; two found no significant difference in symptomatic PE between arms.[55, 98, 99]

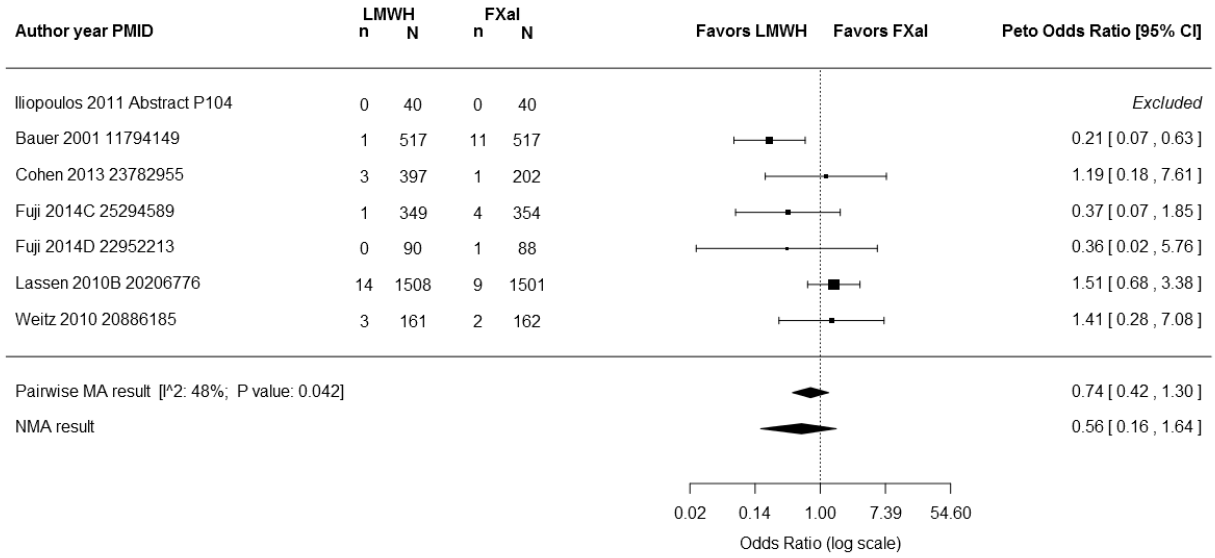
Major Bleeding

Seven RCTs (N=5926) evaluating LMWH and FXaI reported major bleeding (0% to 1.9% in LMWH, 0% to 2.1% in FXaI).[55, 89, 96-100] The rate was lower in the LMWH group in three RCTs,[55, 97, 98] which was statistically significant in one.[97] No major bleeding occurred in either of the groups in one RCT.[89] Meta-analysis of the remaining six RCTs found no significant difference between the two classes for the risk of major bleeding (summary OR=0.74; 95% CI 0.42 to 1.30). There was significant heterogeneity across the RCTs (I^2 = 48%, P = 0.042) (Figure

[d] Since fewer than four RCTs had analyzable data, we did not meta-analyze comparisons in this section, per protocol.

22). Because of the relative rarity of the outcome (generally <1%), meta-analysis was conducted with Peto's fixed effect model; sensitivity analysis with the Mantel-Haenszel method yielded similar results. No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Figure 22. Forest plot: Total knee replacement, major bleeding, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effect model summary estimate (Pairwise meta-analysis [MA] result) and equivalent summary estimate from corresponding network meta-analysis (NMA). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

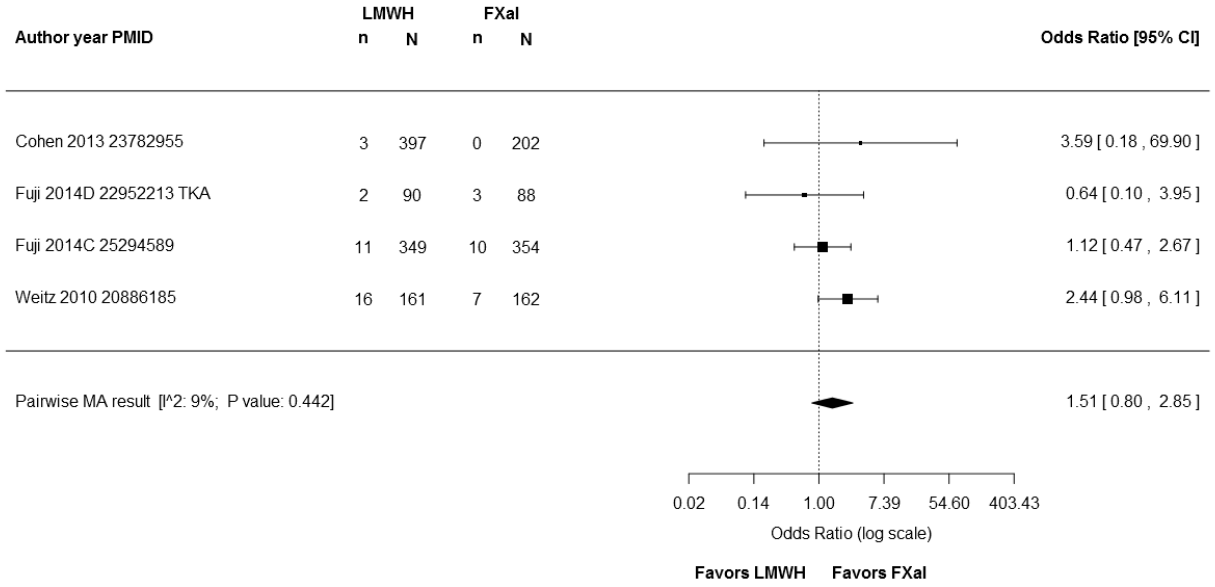
Other Bleeding Events

One RCT reported no fatal bleeding, and found no significant difference in bleeding leading to reoperation between the two classes.[97] Two RCTs found no significant difference in bleeding at surgical site or joint.[96, 98]

Serious Adverse Events (Study-Defined)

Four RCTs (N=1803) reported serious adverse events comparing LMWH (0.8 to 9.9%) versus FXaI (0% to 4.3%).[55, 98-100] Three studies reported a lower rate in the FXaI group.[98-100] Meta-analysis of the four studies yielded no significant difference for the risk of serious adverse events between the two drug classes (summary OR=1.51, 95% CI 0.80 to 2.85). Study results were homogeneous (I^2 = 9%, P = 0.44) (Figure 23).

Figure 23. Forest plot: Total knee replacement, serious adverse events, LMWH versus FXaI



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Other Adverse Events

Three RCTs provided data of 30-day mortality, but one had no deaths; two found no significant difference between intervention classes.[55, 96, 97] One study reported no significant difference in wound complications.[87] One study found no significant difference in readmission due to bleeding or infection.[94]

Adherence

Two RCTs reported adherence for the comparison of LMWH and FXaI (Appendix Table F2). Adherence was defined as taking over 80 percent of the drugs as prescribed in one RCT.[24] The rate of adherence in this RCT was 99 percent (2595/2626) in the FXaI group, and 100 percent (2647/2659) in the LMWH group at 34 days of followup. The other RCT[56] did not define adherence, but reported 100 percent adherence (85/85 in the 15 mg group and 89/89 in the 30 mg group) in the FXaI group and 95 percent (83/87) in the LMWH group during followup for 11 to 14 days.

Key Question 1 (TKR): LMWH Versus FXIi

One RCT (N=216) compared LMWH versus FXIi.[101] The study found no significant difference between the two classes in total VTE, symptomatic VTE, total DVT, symptomatic DVT, and proximal DVT. The study had no occurrences of fatal PE or symptomatic PE.

The study had no major bleeding events. It found no difference in serious adverse events between intervention classes. The study did not report adherence data.

Key Question 1 (TKR): LMWH Versus Mechanical Devices

One RCT (N=229) compared LMWH versus a mechanical device.[102] The study found no significant difference in fatal PE, total DVT, and proximal DVT. There were no fatal bleeding events and 30-day mortality was not significantly different between interventions. No adherence data were reported.

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between LMWH and mechanical devices (OR 0.72, 95% CI 0.42 to 1.23), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F5).[35]

Key Question 1 (TKR): LMWH Versus UFH

Two RCTs (N=638) compared LMWH versus UFH.[103, 104]Both reported on total PE, but one had no PE events; the other study found no significant difference between classes. This latter study also found no significant difference in fatal PE. Both studies found no significant difference in total DVT and proximal DVT. One study also reported no significant difference in symptomatic DVT.

One study found no significant difference between the two classes in major bleeding and bleeding at surgical site or joint. No adherence data were reported.

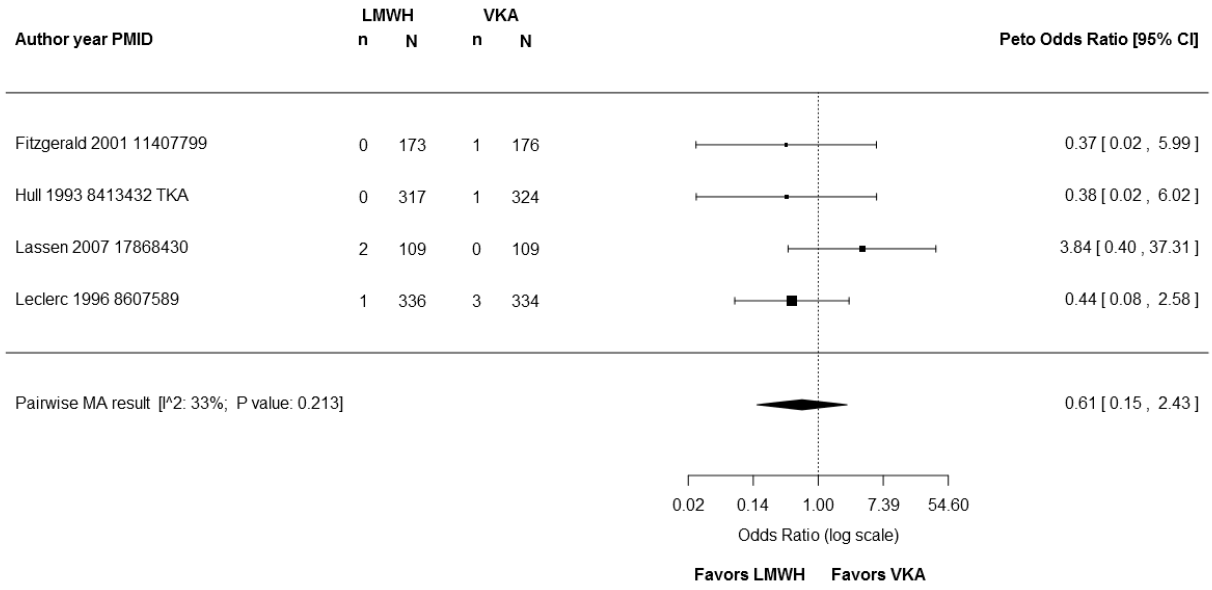
Key Question 1 (TKR): LMWH Versus VKA

Four RCTs (N=1960) compared LMWH versus VKA.[80, 105, 106] All four reported on VTE-related outcomes.

Total PE

Four RCTs (N=1878) reported total PE for the comparison of LMWH and VKA (0% to 1.8% in LMWH, 0% to 0.9% in VKA).[80, 105-107] Three RCTs[80, 105, 106] had a lower rate in the LMWH group. Meta-analysis of the four RCTs found an imprecise, nonsignificant estimate of OR for the risk of total PE between the two drug classes (summary OR=0.61, 95% CI 0.15 to 2.43). Study results were homogeneous (I^2 = 33%, P = 0.21) (Figure 24). Because of the relative rarity of the outcome (generally <1%), meta-analysis was conducted with Peto's fixed effect model; sensitivity analysis with the Mantel-Haenszel method yielded similar results.

Figure 24. Forest plot: Total knee replacement, total pulmonary embolism, LMWH versus VKA

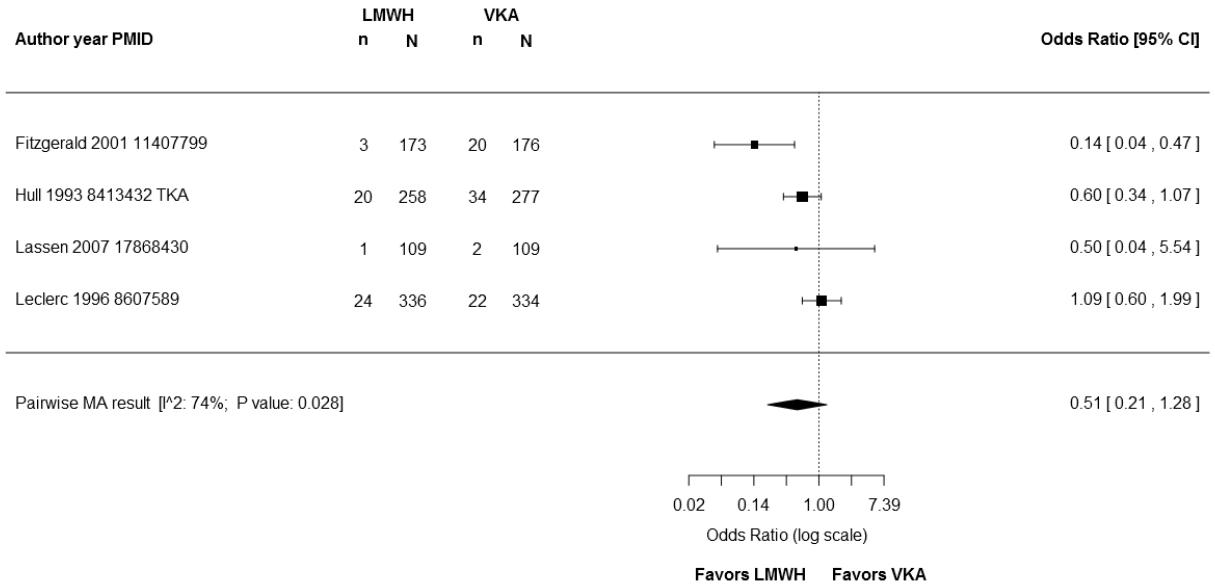


Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effect model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Proximal DVT

Four RCTs[80, 105-107] (N=1772) comparing LMWH and VKA reported the occurrence of proximal DVT (0.9% to 7.8% in LMWH, 1.8 to 12.3% in VKA). The event rate was lower in the LMWH group in three RCTs,[80, 105, 107] statistically significantly so in one.[105] No significant difference was shown for the risk of proximal DVT between the two groups in the meta-analysis of the four RCTs (summary OR=0.51, 95% CI 0.21 to 1.28). There was substantial heterogeneity across the RCTs (I^2 = 74%, P = 0.028) (Figure 25). No clear explanation of the statistical heterogeneity could be found; however, doses and regimens varied across RCTs.

Figure 25. Forest plot: Total knee replacement, proximal deep vein thrombosis, LMWH versus VKA



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier, VKA = vitamin K antagonist.

Other VTE Events

Two RCTs found no significant difference between the two classes in symptomatic VTE.[80, 106] Three RCTs reported no fatal PE events.[80, 105, 106] Three RCTs all found significantly fewer total DVT in the LMWH group (range of ORs 0.42 [95% CI 0.27 to 0.66] to 0.67 [95% CI 0.48 to 0.94]).[80, 105, 106] One RCT found no significant difference in symptomatic DVT.[107]

Adverse Events

Four RCTs reported major bleeding, but one had no major bleeding events;[e] the remaining three studies found no significant difference between classes.[80, 105-107] Three RCTs reported fatal bleeding, but two studies had no fatal bleeding events; the remaining study found no significant difference between intervention classes.[80, 105, 106] One study reported no episodes of bleeding leading to reoperation, infection leading to reoperation, or reoperation due to bleeding or infection.[105] This study also found no significant differences in bleeding at surgical site and 30-day mortality.[105]

Adherence

No studies reported adherence data.

[e] Since fewer than four RCTs had analyzable data, we did not meta-analyze this comparison, per protocol.

Key Question 1 (TKR): VKA Versus Mechanical Devices

A U.S.-based registry NRCS of 25,388 TKR patients found a significant difference in total PE between warfarin and mechanical devices, favoring warfarin (OR 0.46, 95% CI 0.26 to 0.83), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F5).[35]

Key Question 1 (TKR): VKA Versus FXaI

One RCT (N=270) comparing VKA and FXaI found no significant difference in 30-day or in-hospital mortality, and total VTE between the two groups.[108]

Table 2. Results summary: Total knee replacement, intervention class versus class comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
Antiplatelet vs. FXaI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	**6.46 (1.84, 22.6)**			
	DVT, Symptomatic	1	4.72 (0.22, 99.6)			
	Wound complication	1	0.36 (0.07, 1.89)			
Antiplatelet vs. Mechanical Device	DVT, Total	1	**2.52 (1.20, 5.31)**			
	DVT, Proximal	1	0.52 (0.05, 5.87)			
Antiplatelet vs. VKA	DVT, Total	1	0.88 (0.47, 1.66)			
	DVT, Proximal	1	1.08 (0.42, 2.74)			
DTI vs. FXaI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	No estimate			1 RCT
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. Antiplatelet	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	0.73 (0.34, 1.55)			
	DVT, Symptomatic	1	0.49 (0.04, 5.44)			
	Wound complication	1	1.49 (0.24, 9.07)			
LMWH vs. DTI	PE, Total	2	2.96 (0.12, 72.8)			1 RCT
	PE, Fatal	2	2.96 (0.12, 72.8)			
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	2	**2.30 (1.21, 4.38)**			1 RCT
	DVT, Symptomatic	3	0.67 (0.21, 2.12)	1.00 (0.06, 16.5)	7.96 (0.99, 63.9)	
	DVT, Proximal	2	0.67 (0.29, 1.51)	5.58 (0.66, 47.4)		
	Bleeding, Major	*5 (MA)*	*0.96 (0.43, 2.16)*			1 RCT
	Bleeding, Fatal	2	No estimate			2 RCTs
	Bleeding, Leading to reoperation	1	0.33 (0.03, 3.13)			
	Bleeding, Surgical site/joint	1	**5.49 (1.21, 24.8)**			
	Mortality, 30 day or in-hospital	1	0.99 (0.06, 15.8)			
LMWH vs. FXaI	*VTE, Total*	*4 (MA)*	*1.33 (0.89, 1.99)*			
	VTE, Symptomatic	3	0.25 (0.03, 2.26)	0.82 (0.21, 3.12)	2.02 (0.69, 5.95)	
	PE, Total	5	0.14 (0.02, 1.16)	1.67 (0.40, 7.04)	2.59 (0.29, 23.4)	2 RCTs
	PE, Fatal	5	0.20 (0.01, 4.16)	1.00 (0.06, 16.0)		3 RCTs
	PE, Symptomatic	3	2.07 (0.19, 23.2)	2.97 (0.12, 73.8)		1 RCT
	DVT, Total	*7 (MA)*	***2.09 (1.70, 2.58)***			1 RCT

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI)* †	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	DVT, Symptomatic	*8 (MA)*	*0.99 (0.51, 1.91)*			
	DVT, Proximal	*6 (MA)*	***1.84 (1.07, 3.16)***			
	Bleeding, Major	*7 (MA)*	*0.74 (0.42, 1.30)*			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Bleeding, Leading to reoperation	1	0.50 (0.05, 5.52)			
	Bleeding, Surgical site/joint	2	0.33 (0.07, 1.67)	1.37 (0.55, 3.42)		
	Mortality, 30 day or in-hospital	3	0.20 (0.01, 4.16)	1.50 (0.25, 9.03)		1 RCT
	Adverse event, Serious	*4 (MA)*	*1.51 (0.80, 2.85)*			
	Readmission, bleeding or infection (combined)	1	0.24 (0.03, 2.18)			
	Wound complication	1	0.53 (0.12, 2.29)			
LMWH vs. FXIi	VTE, Total	1	1.28 (0.68, 2.41)			
	VTE, Symptomatic	1	0.98 (0.09, 11.0)			
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	1.28 (0.68, 2.41)			
	DVT, Symptomatic	1	0.98 (0.09, 11.0)			
	DVT, Proximal	1	1.43 (0.44, 4.67)			
	Bleeding, Major	1				1 RCT
	Adverse event, Serious	1	0.28 (0.01, 5.47)			
LMWH vs. Mechanical Device	PE, Fatal	1	0.21 (0.01, 4.32)			
	DVT, Total	1	0.86 (0.48, 1.54)			
	DVT, Proximal	1	0.12 (0.01, 2.23)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.34 (0.04, 3.34)			
LMWH vs. UFH	PE, Total	2	0.20 (0.01, 4.10)			1 RCT
	PE, Fatal	2	0.33 (0.01, 8.08)			
	DVT, Total	2	0.63 (0.42, 0.94)	0.80 (0.41, 1.57)		
	DVT, Symptomatic	1	0.33 (0.01, 8.29)			
	DVT, Proximal	2	0.21 (0.08, 0.56)	0.59 (0.14, 2.56)		
	Bleeding, Major	1	0.99 (0.20, 4.94)			
	Bleeding, Surgical site/joint	1	1.81 (0.60, 5.48)			
LMWH vs. VKA	VTE, Symptomatic	2	1.02 (0.06, 16.4)	3.00 (0.31, 29.0)		
	PE, Total	*4 (MA)*	*0.61 (0.15, 2.43)*			

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	PE, Fatal	3	No estimate			3 RCTs
	DVT, Total	3	**0.42** (**0.27, 0.66**)	**0.60** (**0.43, 0.85**)	**0.67** (**0.48, 0.94**)	
	DVT, Symptomatic	1	1.00 (0.06, 16.2)			
	DVT, Proximal	*4 (MA)*	*0.51 (0.21, 1.28)*			
	Bleeding, Major	4	1.16 (0.39, 3.50)	2.36 (0.71, 7.81)	3.13 (0.84, 11.7)	1 RCT
	Bleeding, Fatal	3	0.34 (0.01, 8.33)			2 RCTs
	Bleeding, Leading to reoperation	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	1	2.11 (0.77, 5.76)			
	Mortality, 30 day or in-hospital	1	0.34 (0.03, 3.25)			
	Return to OR, bleeding or infection (combined)	1	No estimate			1 RCT
	Infection, Leading to reoperation	1	No estimate			1 RCT
FXaI vs. VKA	VTE, Total	1	**0.44** (**0.21, 0.91**)			
	Mortality, 30 day or in-hospital	1	0.19 (0.01, 4.02)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, FXaI = factor Xa inhibitor, VKA = vitamin K antagonist, DTI = direct thrombin inhibitor, LMWH = low molecular weight heparin, FXIi = factor XI inhibitor, UFH = unfractionated heparin.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Antiplatelet vs. FXaI, OR = 6.46 favors FXaI).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Cross-Study Subgroup Analyses

As noted at the start of the *Results* section, studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregression no significant difference (P=0.21) was found between the six industry-funded studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregression. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Key Question 1: Hip Fracture Surgery

The results summary table (Table 3) includes results for all reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 1 (HFx): Antiplatelet Drug Versus Mechanical Devices

One RCT compared an antiplatelet drug versus a mechanical device.[109] No significant differences were found between arms for total PE, total DVT, and symptomatic DVT. No adverse events or adherence data were reported.

Key Question 1 (HFx): Antiplatelet Drug Versus VKA

One RCT compared an antiplatelet drug versus VKA.[110] The study found no significant differences in total PE and fatal PE (all patients with PE died). There was no significant difference in major bleeding events and no patient had a fatal bleed. Adherence data were not reported.

Key Question 1 (HFx): LMWH Versus FXaI

Three RCTs (N=1816) compared LMWH versus FXaI.[25, 111, 112] Two studies evaluated VTE; one found no significant difference in total VTE and no symptomatic VTE events; the other found no significant difference in symptomatic VTE. All three reported on PE. One found no significant difference in total PE; two had no symptomatic PE events; and one study found no difference in fatal PE while another had no fatal PE events. The three studies also reported on DVT. Two of three studies found that patients treated with LMWH were significantly more likely to have total DVTs, but the third study found no significant difference in which more

patients treated with FXaI had total DVT (range of ORs 0.55 [95% CI 0.05 to 5.58] to 3.81 [95% CI 1.22 to 11.9]).

All three studies found no significant difference in major bleeding (range of ORs 0.18 [95% CI 0.01 to 3.91] to 2.07 [95% CI 0.12 to 34.4]). One study found no significant difference in fatal bleeding while a second reported no occurrences of fatal bleeding. One study found no significant difference in bleeding leading to reoperation.

One study found no significant difference in serious adverse events[112] and another no significant difference in 30-day mortality.[111]

No study reported adherence data.

Key Question 1 (HFx): LMWH Versus UFH

One RCT compared LMWH versus UFH.[113] The study found no significant difference in total PEs, with no fatal PEs occurring. Total DVTs were just-significantly more likely to occur in patients treated with LMWH. The study found a similar, but nonsignificant estimate of effect for proximal DVTs.

The study found nonsignificant differences between arms for fatal bleeding and 30-day mortality. No adherence data were reported.

Table 3. Results summary: Hip fracture surgery, intervention class versus class comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
Antiplatelet vs. Mechanical Devices	PE, Total	1	2.92 (0.12, 72.8)			
	DVT, Total	1	1.75 (0.49, 6.26)			
	DVT, Symptomatic	1	1.97 (0.35, 11.2)			
Antiplatelet vs. VKA	PE, Total	1	3.00 (0.12, 75.0)			
	PE, Fatal	1	3.00 (0.12, 75.0)			
	Bleeding, Major	1	0.18 (0.02, 1.63)			
	Bleeding, Fatal	1	No estimate			1 RCT
LMWH vs. FXaI	VTE, Total	1	0.55 (0.05, 5.58)			
	VTE, Symptomatic	2	0.75 (0.36, 1.56)			1 RCT
	PE, Total	1	0.99 (0.43, 2.29)			
	PE, Fatal	2	0.86 (0.31, 2.39)			1 RCT
	PE, Symptomatic	2	No estimate			2 RCTs
	DVT, Total	3	0.55 (0.05, 5.58)	**2.71** (**1.90, 3.87**)	**3.81** (**1.22, 11.9**)	
	DVT, Symptomatic	2	0.99 (0.06, 15.8)			1 RCT
	DVT, Proximal	3	2.00 (0.17, 23.4)	**4.86** (**2.00, 11.8**)		1 RCT
	Bleeding, Major	3	0.18 (0.01, 3.91)	1.04 (0.54, 2.00)	2.07 (0.12, 34.4)	
	Bleeding, Fatal	2	2.96 (0.12, 72.9)			1 RCT
	Bleeding, Leading to reoperation	1	0.66 (0.11, 3.94)			
	Mortality, 30 day or in-hospital	1	1.10 (0.70, 1.72)			
	Adverse event, Serious	1	2.15 (0.41, 11.4)			
LMWH vs. UFH	PE, Total	1	14.3 (0.78, 262)			
	PE, Fatal	1	No estimate			1 RCT
	DVT, Total	1	**3.11** (**1.00, 9.68**)			
	DVT, Proximal	1	3.00 (0.91, 9.94)			
	Bleeding, Fatal	1	0.31 (0.01, 7.86)			
	Mortality, 30 day or in-hospital	1	0.62 (0.10, 3.91)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, VKA = vitamin K antagonist, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Antiplatelet vs. Mechanical Devices, OR = 2.92 favors mechanical devices).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Key Question 2: Comparison of Within-Class Thromboprophylaxis Interventions

Note that network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Key Question 2: Total Hip Replacement

The results summary table (Table 4) includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 2 (THR): LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin versus semuloparin.[114] The study found significantly more total DVTs with enoxaparin than semuloparin, but no significant difference in proximal DVTs.

The study also found significantly more episodes of major bleeding with enoxaparin than semuloparin. No study participants had a fatal bleed. There were no significant differences in 30-day mortality or serious adverse events.

The study did not evaluate adherence.

Key Question 2 (THR): LMWH: Enoxaparin Versus Tinzaparin

One RCT compared the LMWHs enoxaparin versus tinzaparin.[115] All VTE-related outcomes were not significantly different in both arms, including total PE, fatal PE, total DVT, symptomatic DVT, and proximal DVT.

There were also no significant differences in major bleeding and surgical site bleeding, and no fatal bleeding events. There were no significant differences in 30-day mortality or heparin-induced thrombocytopenia.

The study did not evaluate adherence.

Key Question 2 (THR): Mechanical Devices: GCS Versus IPC

Two RCTs (N=161) compared GCS versus IPC; in one RCT all participants also received enoxaparin.[116, 117] One NRCS (N=1533) also compared GCS versus active compression devices (Appendix Table F4).[29] One RCT reported no PEs or symptomatic DVTs. The other RCT found no significant difference in total DVTs. Both RCTs found no significant difference in proximal

Table 4. Results summary: Total hip replacement, within-class intervention versus intervention comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	**1.85** (**1.32, 2.60**)			
	DVT, Proximal	1	1.15 (0.54, 2.42)			
	Bleeding, Major	1	**3.52** (**1.16, 10.7**)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	2.00 (0.18, 22.1)			
	Adverse event, Serious	1	1.35 (0.85, 2.16)			
LMWH: Enoxaparin vs. Tinzaparin	PE, Total	1	2.03 (0.18, 22.6)			
	PE, Fatal	1	3.05 (0.12, 75.2)			
	DVT, Total	1	0.91 (0.57, 1.44)			
	DVT, Symptomatic	1	1.52 (0.25, 9.19)			
	DVT, Proximal	1	1.12 (0.60, 2.08)			
	Bleeding, Major	1	2.04 (0.37, 11.3)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	1	2.04 (0.37, 11.3)			
	Mortality, 30 day or in-hospital	1	3.05 (0.12, 75.2)			
	Heparin-induced thrombocytopenia	1	3.05 (0.12, 75.2)			
Mechanical Devices: GCS vs. IPC	PE, Total	1	No estimate			1 RCT
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	12.3 (0.63, 239)			
	DVT, Proximal	2	3.24 (0.96, 11.0)	3.65 (0.14, 93.3)		

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, GCS = graduated compression stockings, IPC = Intermittent Pneumatic Compression.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Enoxaparin vs. Semuloparin, OR = 1.85 favors semuloparin).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

DVTs. The NRCS did not run statistical analyses, but the 0.4 percent had a PE with an active compression device and 0 percent for GCS.

The studies did not report bleeding, other adverse events, or adherence results.

Key Question 2: Total Knee Replacement

The results summary table (Table 5) includes results for all reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 2 (TKR): LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin versus semuloparin.[114] The study found no significant differences in total or proximal DVTs.

The study also found no significant difference in major bleeding. No study participants had a fatal bleed or 30-day mortality. There was no significant difference in serious adverse events.

The study did not evaluate adherence.

Key Question 2 (TKR): LMWH: Enoxaparin Versus Tinzaparin

One RCT compared the LMWHs enoxaparin versus tinzaparin.[89] However, the study participants had no PEs, DVTs, or major bleeding events. The study did not evaluate adherence.

Key Question 2 (TKR): Mechanical Devices: GCS Versus IPC

One RCT compared GCS versus IPC, in which all participants also received enoxaparin.[117] The study found many more total DVTs in the GCS group than the IPC group (14/35 vs. 0/35; OR 47.9, 95% CI 2.72 to 844), but no significant difference in proximal DVTs (although still favoring IPC).

The study did not report bleeding, other adverse events, or adherence results.

Key Question 2 (TKR): Mechanical Devices: TED Hose Versus Non-TED Mechanical Devices

A U.S.-based registry NRCS of 25,388 TKR patients found no significant difference in total PE between those using TED hose and other mechanical devices (OR 0.48, 95% CI 0.06 to 3.51), controlling for age, sex, anesthesia risk category, and use of general anesthesia (Appendix Table F5).[35]

Key Question 2: Hip Fracture Surgery

The results summary table (Table 6) includes results for all reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 2 (HFx): LMWH: Enoxaparin Versus Dalteparin

One RCT compared the LMWHs enoxaparin versus dalteparin.[118] The study participants had no PEs or symptomatic DVTs. The rates of total DVT and proximal DVT were not significantly different between drugs.

The study found no significant difference in major bleeding or surgical site bleeding between LMWHs.

The study did not evaluate adherence.

Key Question 2 (HFx): LMWH: Enoxaparin Versus Semuloparin

One RCT compared the LMWHs enoxaparin and semuloparin.[114] The study found no significant difference in total DVTs, but significantly more proximal DVTs with enoxaparin.

There was no significant difference in major bleeding between LMWHs and no fatal bleeding events in either arm. Serious adverse events and 30-day mortality were not significantly different between arms.

The study did not evaluate adherence.

Table 5. Results summary: Total knee replacement, within-class intervention versus intervention comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	1.20 (0.89, 1.63)			
	DVT, Proximal	1	0.57 (0.26, 1.27)			
	Bleeding, Major	1	1.35 (0.30, 6.05)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
	Adverse event, Serious	1	1.33 (0.64, 2.76)			
LMWH: Enoxaparin vs. Tinzaparin	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	No estimate			1 RCT
	Bleeding, Major	1	No estimate			1 RCT
Mechanical Devices: GCS vs. IPC (+Enoxaparin both arms)	DVT, Total	1	**47.9** (**2.72, 844**)			
	DVT, Proximal	1	3.09 (0.12, 78.4)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, GCS = graduated compression stockings, IPC = Intermittent Pneumatic Compression.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Enoxaparin vs. Semuloparin, OR = 1.20 favors semuloparin).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Table 6. Results summary: Hip fracture surgery, within-class intervention versus intervention comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
LMWH: Enoxaparin vs. Dalteparin	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	1.89 (0.58, 6.20)			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	0.72 (0.12, 4.49)			
	Bleeding, Major	1	2.03 (0.18, 23.0)			
	Bleeding, Surgical site/joint	1	0.33 (0.01, 8.21)			
LMWH: Enoxaparin vs. Semuloparin	DVT, Total	1	1.38 (0.95, 1.99)			
	DVT, Proximal	1	**2.10** (**1.06, 4.14**)			
	Bleeding, Major	1	0.58 (0.14, 2.46)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.49 (0.09, 2.67)			
	Adverse event, Serious	1	0.94 (0.55, 1.62)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Enoxaparin vs. Dalteparin, OR = 1.89 favors dalteparin).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Key Question 3: Comparison of Dosages and Treatment Durations of Thromboprophylaxis Interventions

Key Question 3: Different Doses or Regimens

The narrative here describes comparisons of doses for each intervention that were addressed by two or more studies. Each of the more than 300 specific comparison-outcome pairs that were evaluated by only a single study are presented only in Appendix F.

Key Question 3 (Dose): Total Hip Replacement

The results summary table (Table 7) includes results for reported comparisons and outcomes from THR RCTs with at least two studies. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. The reader should also refer to Appendix F for comparisons evaluated by only one study.

Key Question 3 (Dose, THR): FXaI

Four RCTs (N=981) comparing FXaI low versus high doses reported total VTE (2.9% to 31.7% for low dose, 2.8 to 21.2% for high dose), as elaborated in Figure 26 and Table 7.[26, 55, 56, 58] The rate was significantly lower in the high dose group in one study.[58] Meta-analysis of the four studies found no significant difference between the two dose groups for the risk of total VTE (summary OR=1.55, 95% CI 0.78 to 3.06) (Figure 26). There was heterogeneity across the studies (I^2 = 58%, P = 0.09). The four RCTs all found only rare instances of major bleeding, between 0 and 2 events (0 to 1.2%) per intervention; therefore no accurate estimates of relative major bleeding rates could be determined.

Key Question 3 (Dose, THR): LMWH

Total DVT

Five RCTs (N=1441) reported total DVT for the comparison of low versus high doses of LMWH (4.9% to 20.0% for low dose, 4.6 to 33.8% for high dose), as elaborated in Figure 27 and Table 7.[72-74, 119, 120] The rate was lower in the low dose group in three of the RCTs and statistically significant in one.[120] The rates were statistically higher for the low dose group in two RCTs.[73, 74] Meta-analysis of the five RCTs yielded an imprecise summary OR of 1.33 (95% CI 0.56 to 3.18) for the risk of total DVT (Figure 27). There was statistical heterogeneity across the RCTs (I^2 = 83%, P <0.01). No clear explanation of the statistical heterogeneity could be found; however, specific drugs, doses, and regimens varied across RCTs.

Proximal DVT

Four RCTs (N=1047) that assessed relative effectiveness of low versus high doses of LMWH reported proximal DVT (2.4 to 4.7% for low dose, 2.1 to 7.5% for high dose), as elaborated in Figure 28 and Table 7.[72, 74, 119, 120] One RCT showed a lower rate in the low dose group.[120] No significant difference was shown for the risk of proximal DVT between the two doses in the meta-analysis of the four RCTs (summary OR=1.04, 95% CI 0.55 to 1.98). Study results were homogeneous (I^2 = 0%, P = 0.47) (Figure 28).

Major Bleeding

Four RCTs (N=1498) that compared low versus high doses of LMWH reported major bleeding (1.2 to 2.9% in low dose group, 2.0% to 4.2% in high dose group), as elaborated in Figure 29 and Table 7.[73, 74, 119, 120] The rate of bleeding was lower in the low dose group in three RCTs.[73, 74, 119] Meta-analysis of the four RCTs yielded a summary OR of 0.42 (95% CI 0.21 to 0.86) for the risk of major bleeding, significantly favoring the low dose group. Study results were homogeneous (I^2 = 0%, P = 0.54) (Figure 29).

Key Question 3 (Dose, THR): Dabigatran

Two RCTs (N=2845) compared different doses (150 mg vs. 220 or 225 mg) of dabigatran.[51, 52] The studies found no significant difference between the two dose groups regarding major bleeding.

Key Question 3 (Dose, THR): Darexaban

Two RCTs (N=835) compared darexaban 15 mg versus 30 mg twice daily.[55, 57] No significant difference was found in total VTE in the two studies.

Two RCTs (N=801) compared darexaban 30 mg versus 60 mg once daily.[57, 58] The studies found no significant difference in total VTE, and reported no fatal PEs.

Key Question 3 (Dose, THR): Edoxaban

Two RCTs (N=536) compared edoxaban 15 mg and 30 mg once daily.[26, 56] The two studies found no significant difference in total VTE and major bleeding, and reported no symptomatic PE events. One RCT reported no proximal DVTs and no serious adverse events.[53] The other found no significant differences in proximal DVTs or in serious adverse events.[59]

Key Question 3 (Dose, THR): Enoxaparin

Two RCTs (N=792) compared enoxaparin 40 mg once daily and 30 mg every 12 hours.[73, 74] The two studies found significantly fewer total DVT in the low dose group, while no significant difference was found in major bleeding.

Key Question 3 (Dose, THR): Intermittent Pneumatic Compression

Three RCTs compared three different regimens of mechanical devices (Appendix Table F1). One RCT (N=54) compared IPC with adjusted versus fixed cycling rates reported adherence.[121] The rate was adjusted every 30 minutes according to the individual refill time of both legs in the first group, while the rate was fixed at 90 cycles per hour in the other group. The study found no significant difference in total DVT, proximal DVT, and adherence between the two groups. During followup, 100 percent of patients received full-time pneumatic compression as scheduled (good adherence) in both groups.

One RCT (N=24) compared IPC with alternate sequential compression versus continuous sequential compression of both legs.[122] The study found no significant difference in total DVT, and reported no proximal DVT and no symptomatic DVT events.

One RCT (N=423) compared two different IPC devices with different methods of compression (rapid inflation, asymmetrical compression vs. sequential circumferential compression).[123] The study found significant fewer total DVT with the rapid inflation, asymmetrical compression device, but found no significant difference in total PE, proximal

DVT, and 30-day mortality. The study reported no fatal PE, symptomatic DVT, and no fatal bleeding.

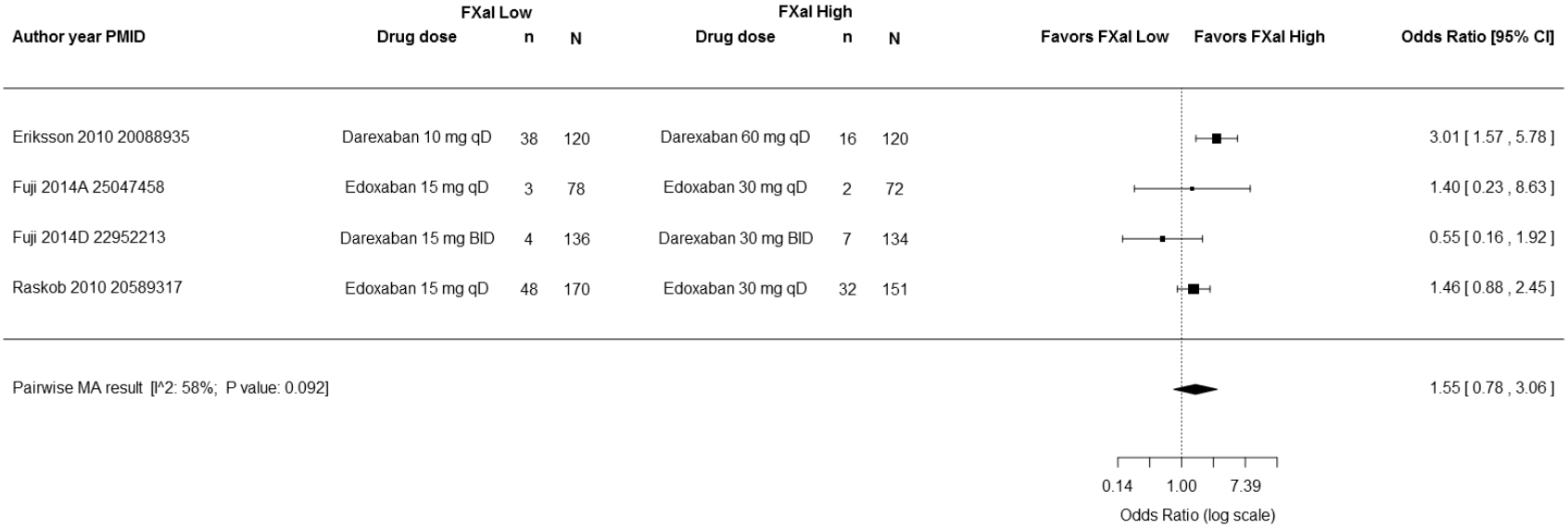
Table 7. Results summary: Total hip replacement, dose comparisons

Comparison (**Daily Dose**)	**Outcome**	**Studies, N**	**Patients, N**	**OR (95% CI), 1*** ***or Summary OR (95% CI)*** †	**OR (95% CI), 2***	**OR (95% CI), 3***	**No Events**‡
FXaI: Darexaban 5, 10, 30, 60, 120 mg Edoxaban 15, 30, 60, 90 mg	VTE, Total	4 (MA)	981	*1.55 (0.78, 3.06)*			
LMWH: Certoparin 3000, 5000 IU Dalteparin 2500, 5000 IU Enoxaparin 40, 60 mg	DVT, Total	5 (MA)	1441	*1.33 (0.56, 3.18)*			
	DVT, Proximal	4 (MA)	1047	*1.04 (0.55, 1.98)*			
	Bleeding, Major	4 (MA)	1498	***0.42 (0.21, 0.86)***			
Dabigatran 150 mg vs. Dabigatran 220 or 225 mg	Bleeding, Major	2	2845	0.64 (0.33, 1.23)	0.84 (0.36, 1.98)		
Darexaban 15 mg BID vs. Darexaban 30 mg BID	VTE, Total	2	835	0.55 (0.16, 1.92)	1.47 (0.90, 2.41)		
Darexaban 30 mg qD vs. Darexaban 60 mg qD	VTE, Total	2	801	1.02 (0.62, 1.65)	1.55 (0.77, 3.14)		
	PE, Fatal	2	801	No estimate			2 RCTs
Edoxaban 15 mg vs. Edoxaban 30 mg	VTE, Total	2	471	1.40 (0.23, 8.63)	1.46 (0.88, 2.45)		
	PE, Symptomatic	2	471	No estimate			2 RCTs
	DVT, Proximal	2	471	2.02 (0.69, 5.95)			1 RCT
	Bleeding, Major	2	536	0.31 (0.01, 7.83)	0.88 (0.05, 14.3)		
	Adverse event, serious	2	536	1.43 (0.46, 4.47)			1 RCT
Enoxaparin 30 mg vs. Enoxaparin 40 mg	DVT, Total	2	791	**0.28** (**0.13, 0.61**)	**0.28** (**0.13, 0.61**)		
	Bleeding, Major	2	792	2.85 (0.75, 10.9)	2.88 (0.75, 11.0)		

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: BID = twice daily, DVT = deep vein thrombosis, PE = pulmonary embolism, qD = daily, VTE = venothromboembolism.

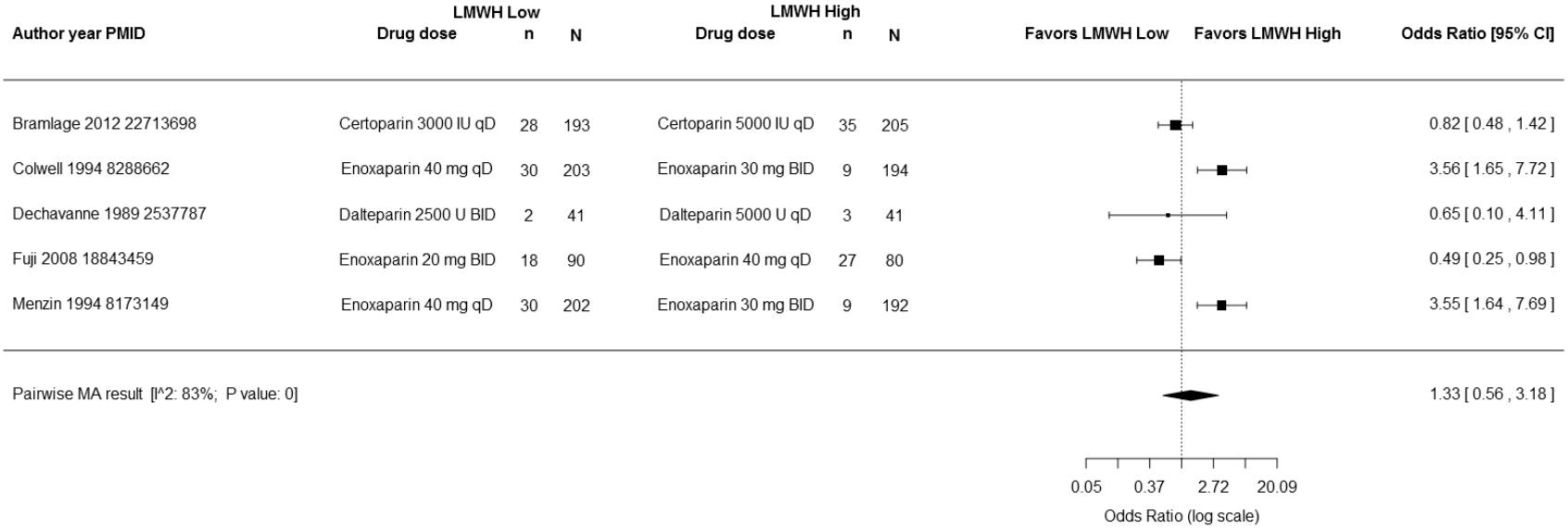
* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for FXaI, OR = 1.55 favors higher dose).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Figure 26. Forest plot: Total hip replacement, total venothromboembolism, FXaI, low versus high dose



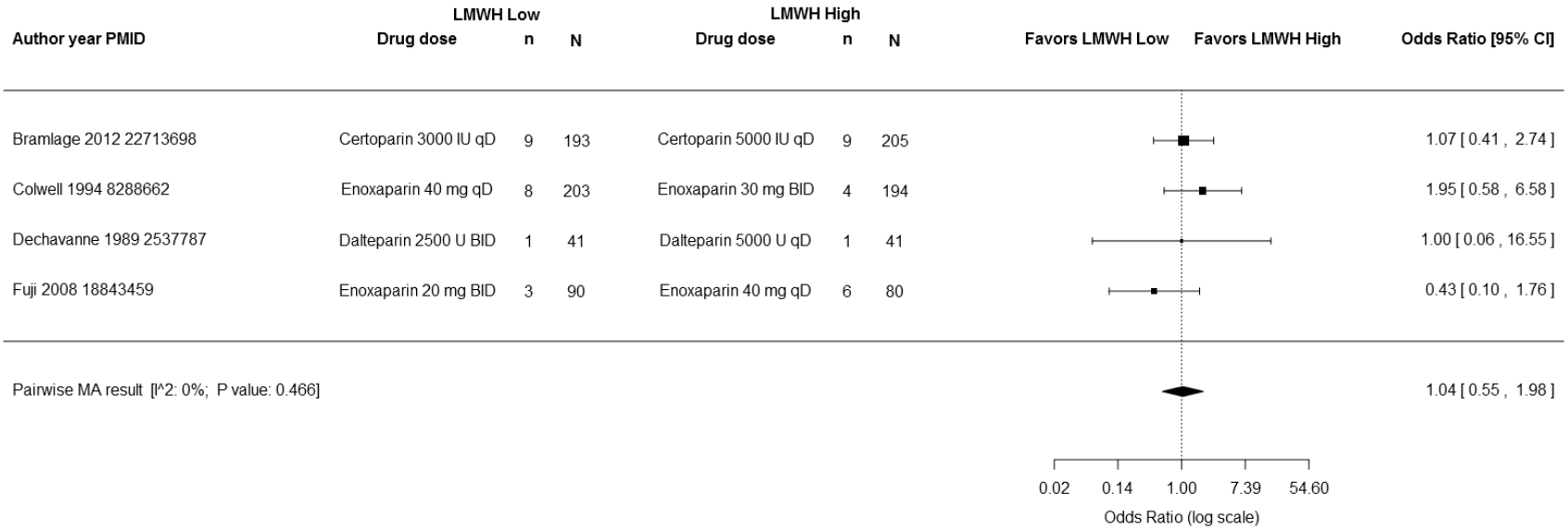
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, PMID = PubMed identifier, VTE = venothromboembolism.

Figure 27. Forest plot: Total hip replacement, total deep vein thrombosis, LMWH, low versus high dose



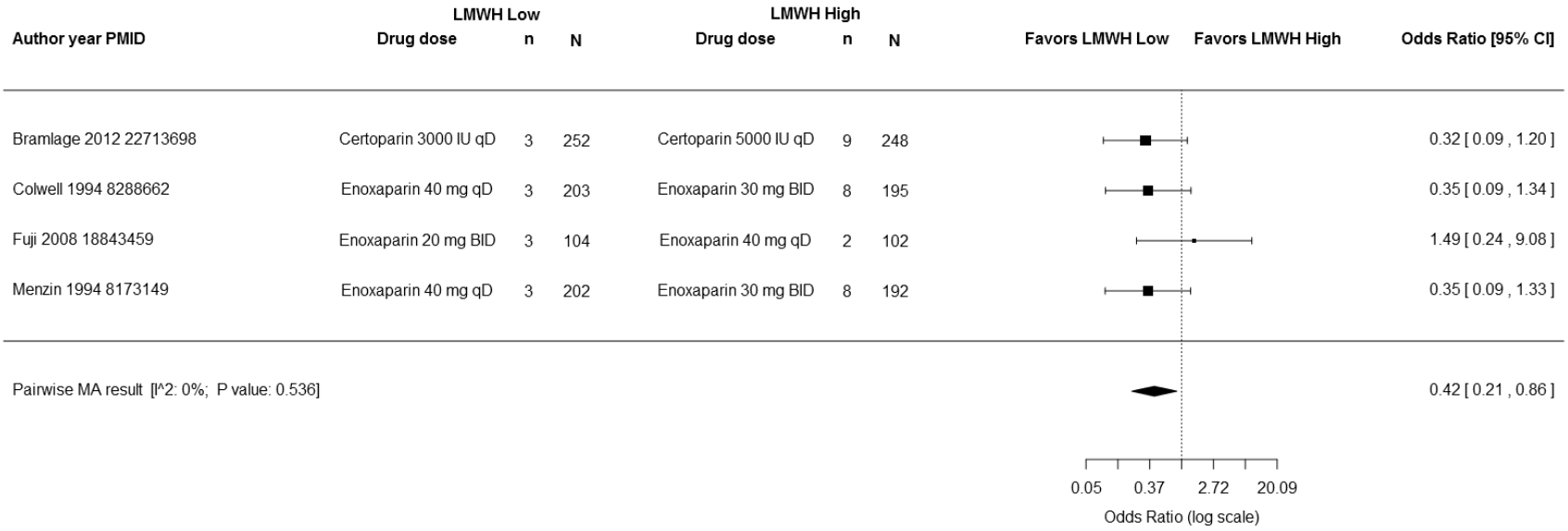
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Figure 28. Forest plot: Total hip replacement, proximal deep vein thrombosis, LMWH, low versus high dose



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Figure 29. Forest plot: Total hip replacement, major bleeding, LMWH, low versus high dose



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PMID = PubMed identifier.

Key Question 3 (Dose): Total Knee Replacement (TKR)

The results summary table (Table 8) is presented at the end of the TKR section. It includes results for reported comparisons and outcomes from TKR RCTs with at least two studies. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. The reader should also refer to Appendix Table F2 for comparisons evaluated by only one study.

Key Question 3 (Dose, TKR): DTI

Total DVT

Three RCTs[52, 65, 124] (N=577) comparing high versus doses of DTIs (dabigatran 150 mg daily vs. 220 mg daily) reported on total DVT. Two studies showed nonsignificant differences between groups (range of ORs 1.54 [95% CI 0.83 to 2.87] to 1.85 [95% CI 0.97 3.54]), while one study found significantly increased risk in the low dose group (OR=2.08, 95% CI 1.13 to 3.83).

Symptomatic DVT

Four RCTs[65, 91, 92, 124] (N=3141) reported symptomatic DVT for the comparison of low versus high doses of DTI (0.4 to 1.6% in low dose, 0.1 to 1.2% in high dose), as elaborated in Figure 30 and Table 8. The event rate was higher in the low dose group in two studies.[65, 91] No difference was shown between the two groups by meta-analysis of the four RCTs (summary OR=1.14, 95% CI 0.49 to 2.65). The study results were homogeneous (I^2=0%, P value=0.71) (Figure 30). Because of the relative rarity of the outcome (generally <1%), meta-analysis was conducted with Peto's fixed effect model; sensitivity analysis with the Mantel-Haenszel method yielded similar results.

Proximal DVT

Four RCTs[52, 65, 92, 124] (N=1860) comparing low versus high doses of DTI reported proximal DVT (1.7 to 3.2% in low dose, 0% to 2.3% in high dose), as elaborated in Figure 31 and Table 8. The rate of proximal DVT was higher in the low dose group in all four studies. Meta-analysis of the four RCTs yielded a nonsignificant difference between the two dose groups (summary OR=1.57, 95% CI 0.83 to 2.96). The study results were homogeneous (I^2=0%, P value=0.72) (Figure 31).

Other VTE

One RCT comparing different doses of DTI found no significant difference in total VTE between the two dose groups. Three RCTs[65, 91, 124] reported on total PE for the comparison of low versus high dose of DTI (N=1888). Two studies reported no PE events, and one study found no significant difference between groups (OR=2.91, 95% CI 0.12 to 71.7). Two studies reported no fatal PE in either comparison groups.[65, 91]

Major Bleeding

Five RCTs (N=3875) reported major bleeding for the comparison of low versus high doses for DTI (0% to 1.3% in low dose, 0.6 to 4.8% in high dose), as elaborated in Figure 32 and Table 8.[52, 65, 91, 92, 124] Three RCTs[52, 92, 124] had a lower rate in the low dose group. No significant difference was shown for the risk of major bleeding between the two doses by meta-analysis of

the five RCTs (summary OR=0.65, 95% CI 0.34 to 1.24). Study results were homogeneous (I^2 = 0%, P = 0.43) (Figure 32).

Adverse Events

Four RCTs[65, 91, 92, 125] (N=3354) that compared DTIs of difference doses (dabigatran 150 mg daily vs. 220 mg daily) reported 30-day or in-hospital mortality; one reported no events, and the other two found no significant difference between the two dose groups (range of ORs 0.97 [95% CI 0.06 to 15.5] to 0.98 [95% CI 0.06 to 15.8]). Two RCTs (N=1990) that reported surgical site or joint bleeding found no significant difference between groups (range of ORs 0.32 [95% CI 0.01 to 7.95] to 1.48 [95% CI 0.25 to 8.86]).[92, 125] One RCT reported no wound infection in either dose groups.[124]

Key Question 3 (Dose, TKR): FXaI

Total VTE

Five RCTs (N=1053) that examined relative effectiveness of low versus high doses of FXaI reported total VTE (15.3 to 28.8% in low dose, 8.8 to 15.5% in high dose), as elaborated in Figure 33 and Table 8.[55, 99, 100, 126, 127] Patients who received FXaI at high doses had a lower rate of VTE in all the RCTs, which was statistically significant in two.[100, 126] Meta-analysis of the five RCTs yielded a summary OR of 2.06 (95% CI 1.48 to 2.86) for the risk of total VTE, significantly favoring the high dose group. Study results were homogeneous (I^2 = 0%, P = 0.92) (Figure 33).

Symptomatic DVT

Four RCTs (N=802) assessing low versus high doses of FXaI reported the outcome of symptomatic DVT (1.0% to 3.6% in low dose, 0% to 0.8% in high dose).[55, 99, 100, 126] One RCT reported no events; the other three had a lower rate in the high dose group (range of ORs 2.93 [95% CI 0.12 to 73.0] to 4.38 [95% CI 0.48 to 39.7]).

Proximal DVT

Four RCTs (N=784) that assessed low versus high doses of FXaI reported proximal DVT (0% to 6.0% in low dose, 0.8 to 1.8% in high dose), as elaborated in Figure 34 and Table 8.[55, 99, 100, 126] The rate was lower in the high dose group in three RCTs.[55, 99, 100] Meta-analysis of the four RCTs yielded no significant difference for the risk of proximal DVT between the two doses (summary OR=2.51, 95% CI 0.85 to 7.42). Study results were homogeneous (I^2 = 0%, P = 0.54) (Figure 34).

Major Bleeding

Four RCTs (N=1095) that compared low versus high doses of FXaI reported major bleeding (0% to 1.2% in low dose, 0% to 1.1% in high dose).[55, 99, 100, 126] One study reported no events; the rate was lower in the high dose group in two RCTs[99, 100] but lower in one RCT (range of ORs 0.32 [95% CI 0.01 to 7.84 to 5.03 [95% CI 0.24 to 105]).[55]

Other Adverse Events

Two RCTs (N=454) that compared different doses of FXaIs reported no 30-day or in-hospital mortality in either arms.[55, 127]

Key Question 3 (Dose, TKR): Dabigatran

Three RCTs (N=3365) compared dabigatran 150 mg daily and 220 mg daily.[65, 91, 92] Two studies reported total PEs, but one had no PE events; the other found no significant difference in PE events. Two studies reported no fatal PE events. The three RCTs found no significant difference in symptomatic DVT (range of ORs 0.80 [95% CI 0.27 to 2.38] to 2.92 [95% CI 0.30 to 28.1]). Two studies found no significant difference in proximal DVT.

The three RCTs found no significant difference in major bleeding (range of ORs 0.14 [95% CI 0.01 to 2.79] to 0.98 [95% CI 0.28 to 3.41]), and reported no fatal bleeding. The three studies reported bleeding leading to reoperation, but one had no such events; the remaining two found no significant differences. The three studies also reported 30-day mortality, with no mortality in one and no significant difference in two.

Key Question 3 (Dose, TKR): Edoxaban

One RCT[56] comparing high versus low doses of edoxaban reported adherence. At 11 to 14 days of followup, 100 percent of patients were adherent to their prescriptions in both dose groups.

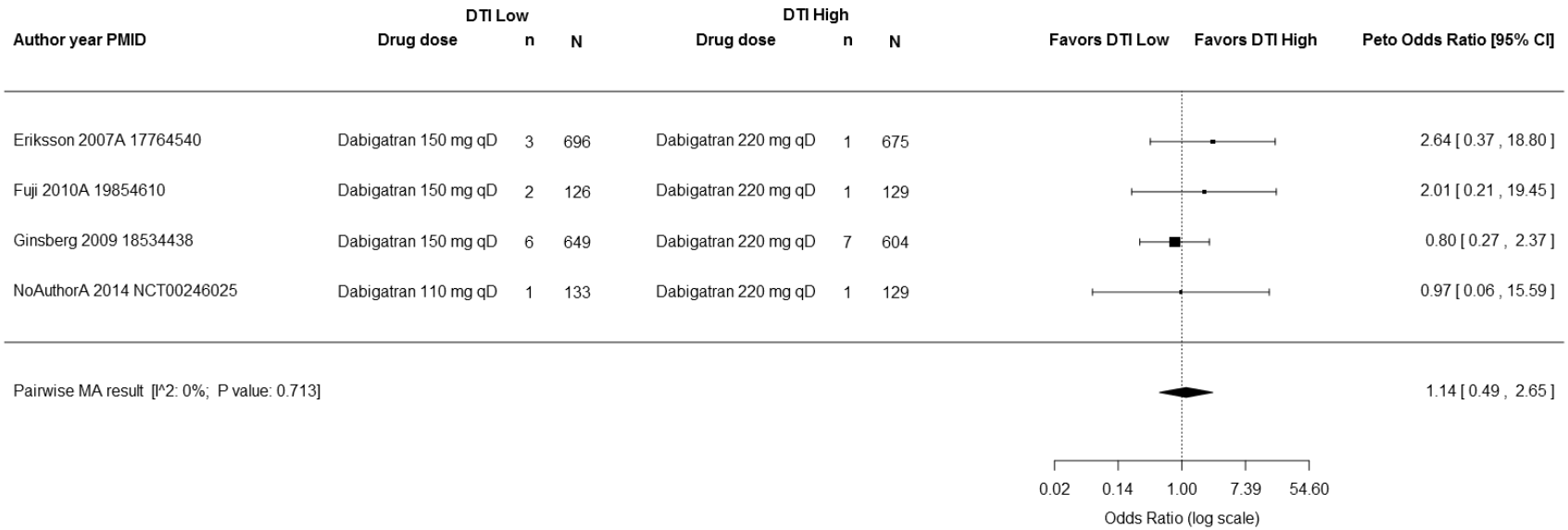
Table 8. Results summary: Total knee replacement, dose comparisons

Comparison (**Daily Dose**)	**Outcome**	**Studies, N**	**Patients, N**	**OR (95% CI), 1*** ***or Summary OR (95% CI) †***	**OR (95% CI), 2***	**OR (95% CI), 3***	**No Events‡**
DTI: Dabigatran 50, 110, 150, 220 mg	PE, Total	3	1888	2.91 (0.12, 71.7)			2 RCTs
	DVT, Total	3	577	1.54 (0.83, 2.87)	1.85 (0.97, 3.54)	2.08 (1.13, 3.83)	
	DVT, Symptomatic	4 (MA)	3141	*1.14 (0.49, 2.65)*			
	DVT, Proximal	4 (MA)	1860	*1.57 (0.83, 2.96)*			
	Bleeding, Major	5 (MA)	3875	*0.65 (0.34, 1.24)*			
	Mortality, 30 day or in-hospital	3	3354	0.97 (0.06, 15.5)	0.98 (0.06, 15.8)		1 RCT
	Bleeding, Surgical site/Joint	2	1990	0.32 (0.01, 7.95)	1.48 (0.25, 8.86)		
FXaI: Darexaban 15, 30 mg Edoxaban 5, 15, 30, 60 mg Erixaban 0.1, 0.3, 0.5, 1, 2.5, 4, 10 mg TAK-442 20, 40, 80, 160 mg	VTE, Total	5 (MA)	1053	***2.06 (1.48, 2.86)***			
	DVT, Symptomatic	4	806	2.93 (0.12, 73.0)	3.26 (0.13, 80.9)	4.37 (0.48, 39.7)	1 RCT
	DVT, Proximal	4 (MA)	779	*2.51 (0.85, 7.42)*			
	Bleeding, Major	4	1095	0.32 (0.01, 7.84)	2.2 (0.2, 24.5)	5.03 (0.24, 106)	1 RCT
	Mortality, 30 day or in-hospital	2	454	No estimate			2 RCT
Dabigatran 150 mg vs. Dabigatran 220 mg	PE, Total	2	1626	2.91 (0.12, 71.7)			1 RCT
	PE, Fatal	2	1626	No estimate			2 RCTs
	DVT, Symptomatic	3	2879	0.80 (0.27, 2.38)	2.06 (0.18, 23.1)	2.92 (0.30, 28.1)	
	DVT, Proximal	2	1468	1.34 (0.67, 2.68)	4.60 (0.22, 96.9)		
	Bleeding, Major	3	3365	0.14 (0.01, 2.79)	0.87 (0.35, 2.15)	0.98 (0.28, 3.41)	
	Bleeding, Fatal	3	3365	No estimate			3 RCTs
	Bleeding, Leading to reoperation	3	3365	0.32 (0.03, 3.09)	0.34 (0.01, 8.39)		1 RCT
	Bleeding, Surgical site/Joint	2	1990	0.32 (0.01, 7.95)	1.48 (0.25, 8.86)		
	Mortality, 30 day or in-hospital	3	3354	0.97 (0.06, 15.5)	0.98 (0.06, 15.8)		1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, mg = milligram.

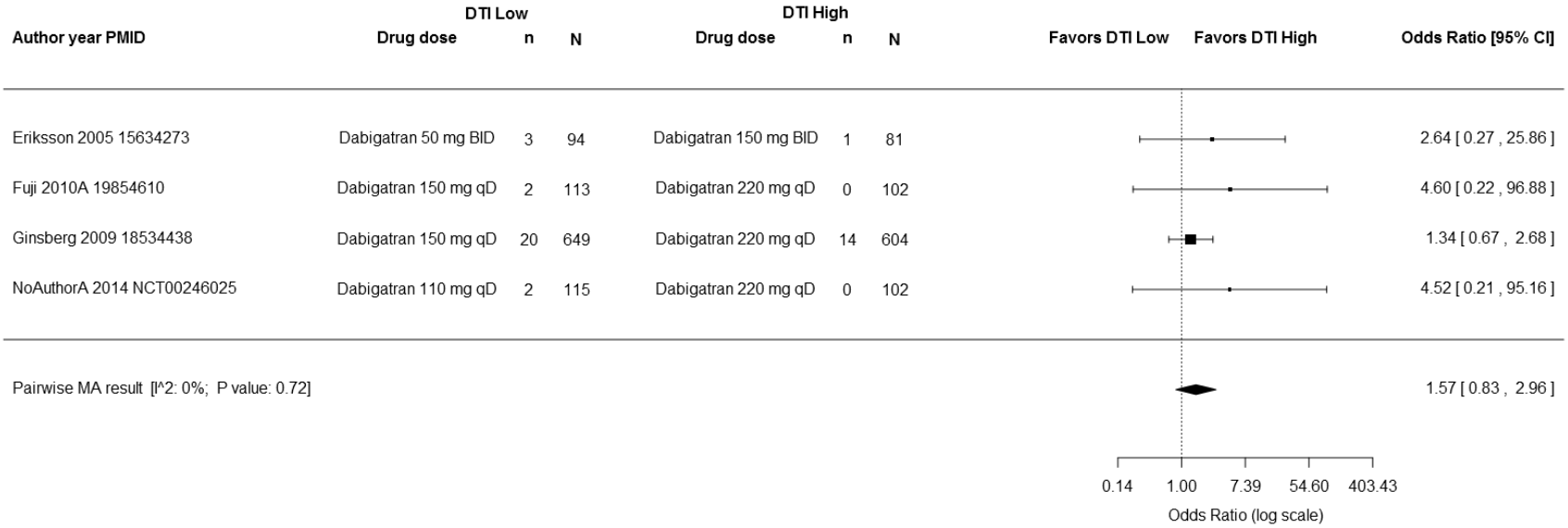
* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for DTI, OR = 2.91 favors higher dose).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Figure 30. Forest plot: Total knee replacement, symptomatic deep vein thrombosis, DTI, low versus high dose



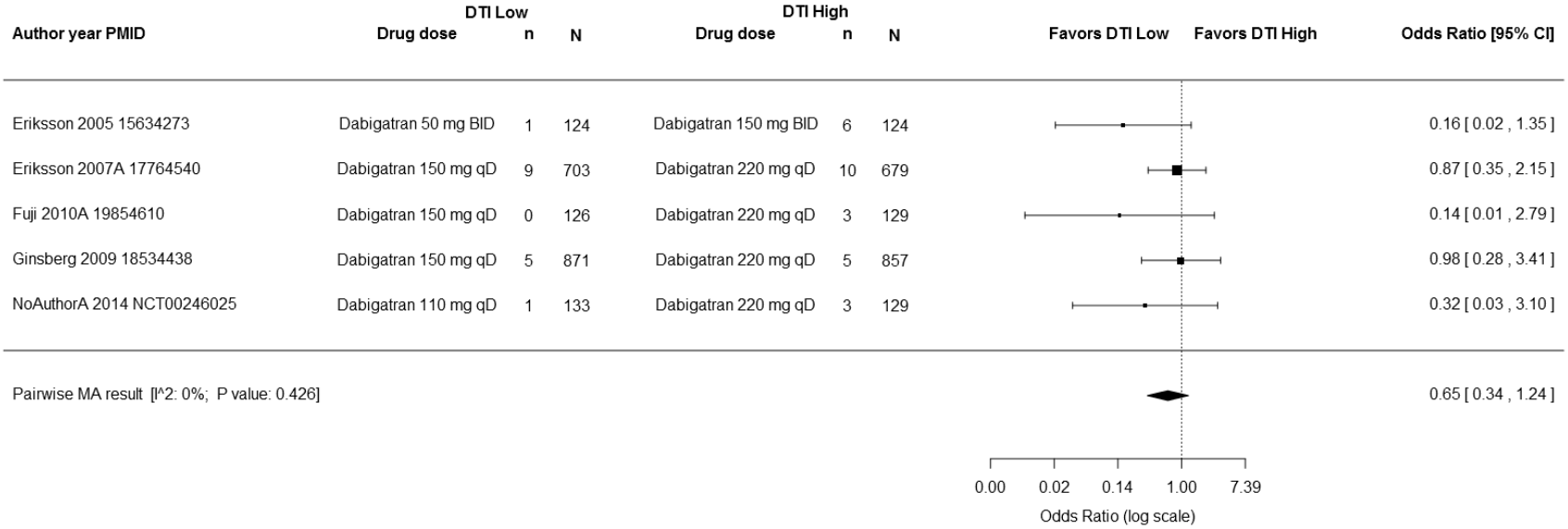
Forest plot of randomized controlled trials with calculated Peto odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with Peto fixed effect model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, PMID = PubMed identifier.

Figure 31. Forest plot: Total knee replacement, proximal deep vein thrombosis, DTI, low versus high dose



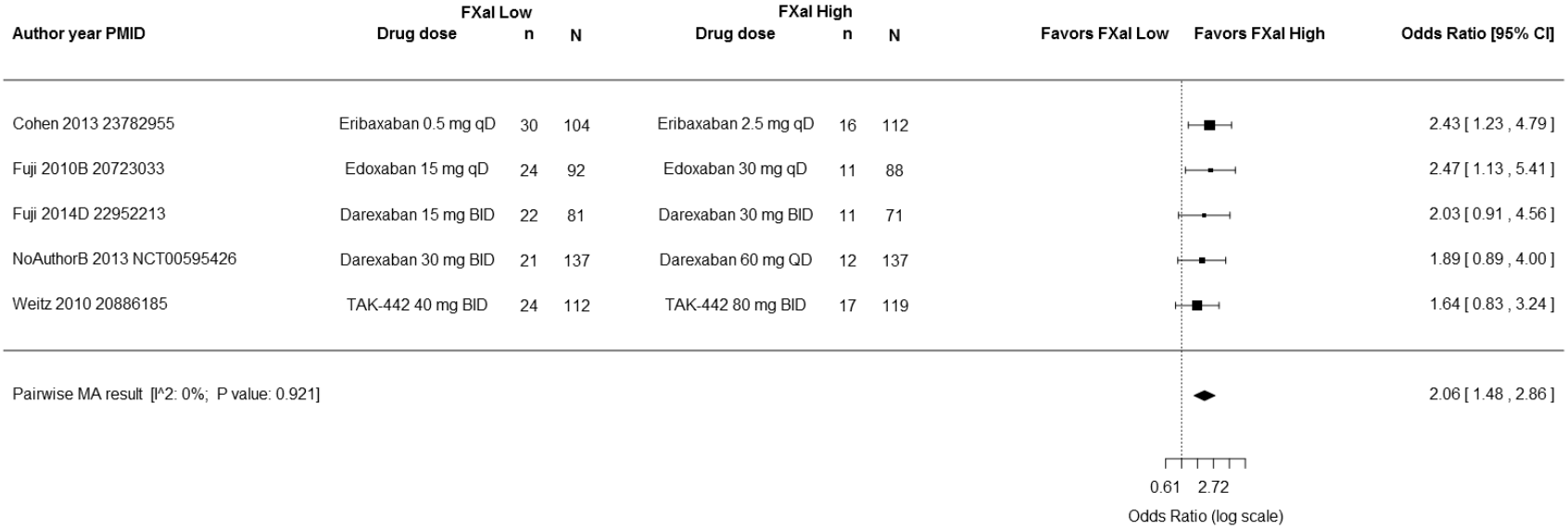
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, PMID = PubMed identifier.

Figure 32. Forest plot: Total knee replacement, major bleeding, DTI, low versus high dose



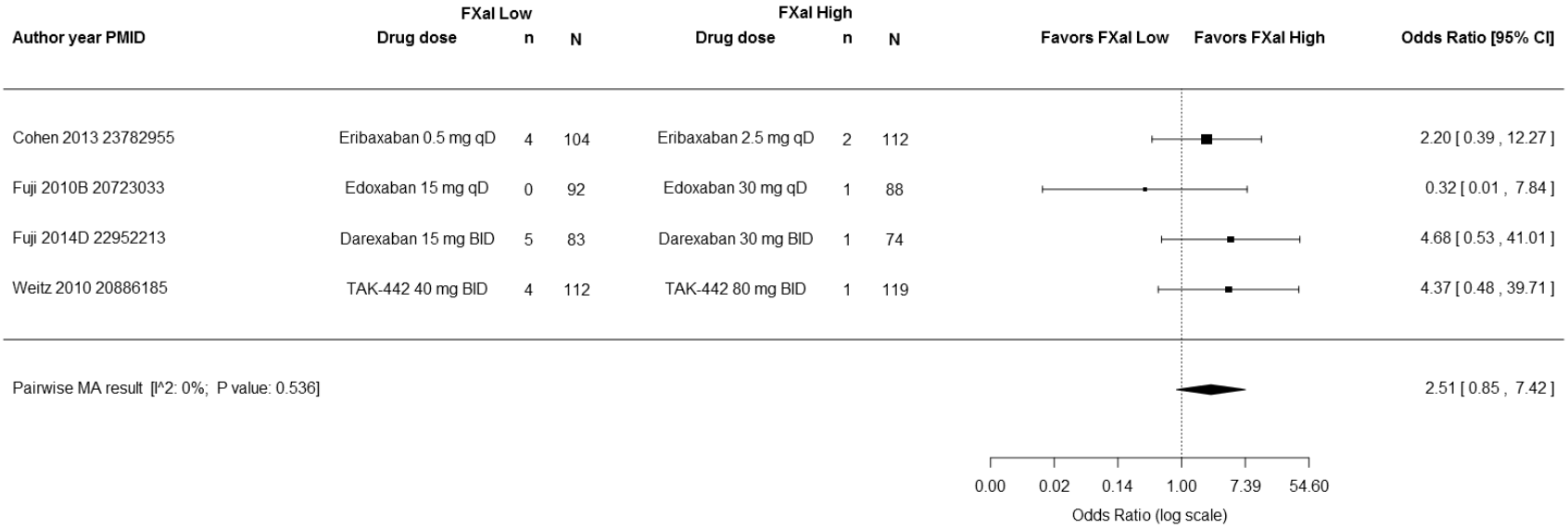
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DTI = direct thrombin inhibitor, PMID = PubMed identifier.

Figure 33. Forest plot: Total knee replacement, total venothromboembolism, FXaI, low versus high dose



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: FXaI = factor Xa inhibitor, PMID = PubMed identifier, VTE = venous thromboembolism.

Figure 34. Forest plot: Total knee replacement, proximal DVT, FXaI, low versus high dose



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, PMID = PubMed identifier.

Key Question 3 (Dose): Hip Fracture Surgery

None of the studies of HFx surgery compared different intervention doses or regimens.

Key Question 3: Different Treatment Durations

Key Question 3 (Duration): Total Hip Replacement

The results summary table (Table 9) includes results for reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. NRCS are summarized in Appendix Table F4

Key Question 3 (Duration, THR): Various Anticoagulation Interventions

Two NRCSs reported on total VTE in patients undergoing THR (Appendix Table F4). Both evaluated different durations of treatment in large cohorts who had received a variety of anticoagulation types. Wells 2010 reported no significant differences among anticoagulation durations of 14, 21, and 28 days that favored longer prophylaxis.[40] Pedersen 2015 reported slightly fewer VTE events with anticoagulation of more than 28 days than with short (0 to 6 days) or standard (7 to 27 days) duration. Once adjusted for age, sex, Charlson Comorbidity Index score, anticoagulation drug and use of acetylsalicylic acid, other antiplatelet drugs, and warfarin use prior to THR, no significant differences were found between short and extended duration (>28 days; HR 0.83, 95% CI 0.52 to 1.31) or between standard and extended durations (HR 0.82, 95% CI 0.50 to 1.33).[30]

In an NRCS, Wells 2010 compared PE rates across timepoints of varied anticoagulant interventions (Appendix Table F4). The NRCS reported no significant differences among anticoagulation durations of 14, 21, and 28 days.[40]

In a NRCS, Wells 2010 compared DVT rates across timepoints of varied anticoagulant interventions.[40] The NRCS reported no significant differences among anticoagulation durations of 14, 21, and 28 days (Appendix Table F4).

Key Question 3 (Duration, THR): FXaI

One RCT (N=40) compared rivaroxaban given for short and long durations,[59] but reported no total DVTs.

Key Question 3 (Duration, THR): LMWH

Six RCTs (N=1463) compared LMWH of short versus long durations.[128-133]

Total PE

Five RCTs (N=1128) reported total PE for the comparison of short versus long therapeutic durations of LMWH (0% to 6.6% for short duration, 0% to 3.6% for long duration), as elaborated in Figure 35.[128-132] One RCT reported no occurrence of PE in either comparison group.[130] Patients who received LMWH for long duration had a lower event rate in the remaining four RCTs. Meta-analysis of the four RCTs found an almost-significant difference between the two treatment durations for the risk of total PE (summary OR=2.35, 95% CI 0.83 to 6.62), favoring long duration (Figure 35). Study results were homogeneous (I^2 = 0%, P = 0.94).

Total DVT

Six RCTs (N=1308) reported total DVT and examined short versus long therapeutic durations of LMWH (11.8% to 32.8% for short duration, 4.4 to 16.0% for long duration).[128-133] Patients who received LMWH of long duration had a lower event rate in all the RCTs, statistically significantly so in four.[128-131] Meta-analysis of the six RCTs yielded a summary OR of 2.87 (95% CI 2.08 to 3.96) for the risk of total DVT, significantly favoring the long duration group. Study results were homogeneous (I^2 = 0%, P = 0.96) (Figure 36).

Proximal DVT

Five RCTs (N=1300) reported proximal DVT for the comparison of short versus long therapeutic durations of LMWH (5.0% to 21.4% for short duration, 0.9% to 8.8% for long duration).[128-131, 133] The rate was lower in the long duration group in all the RCTs, which was statistically significant in two.[128, 129] Meta-analysis of the five RCTs yielded a summary OR of 2.94 (95% CI 1.62 to 5.33) for the risk of proximal DVT, significantly favoring the long duration group. Study results were homogeneous (I^2 = 38%, P = 0.19) (Figure 37).

Other VTE Events

Two RCTs found significantly fewer symptomatic VTE in the long duration group.[128, 129] Four RCTs reported fatal PE; one found no significant difference, and three reported no incidents of fatal PE.[128-131] Three RCTs found no significant difference in symptomatic DVT.[129, 131, 132]

Adverse Events

Three RCTs reported on major bleeding, with no significant difference in one and no incidents of major bleeding in two studies.[128, 130, 133] Four studies reported no fatal bleeding. Three RCTs reported 30-day mortality; one found no significant difference, and two reported no mortality.[128, 130, 131] One study found no significant difference in reoperation due to bleeding or infection.[132]

Adherence

No study reported on adherence

Key Question 3 (Duration, THR): VKA

One RCT (N=360) compared short versus long therapeutic durations of warfarin.[134] The study found no significant difference in symptomatic VTE, total PE, total DVT, symptomatic DVT, proximal DVT, and major bleeding, and reported no fatal PE and no fatal bleeding. The study did not report on adherence.

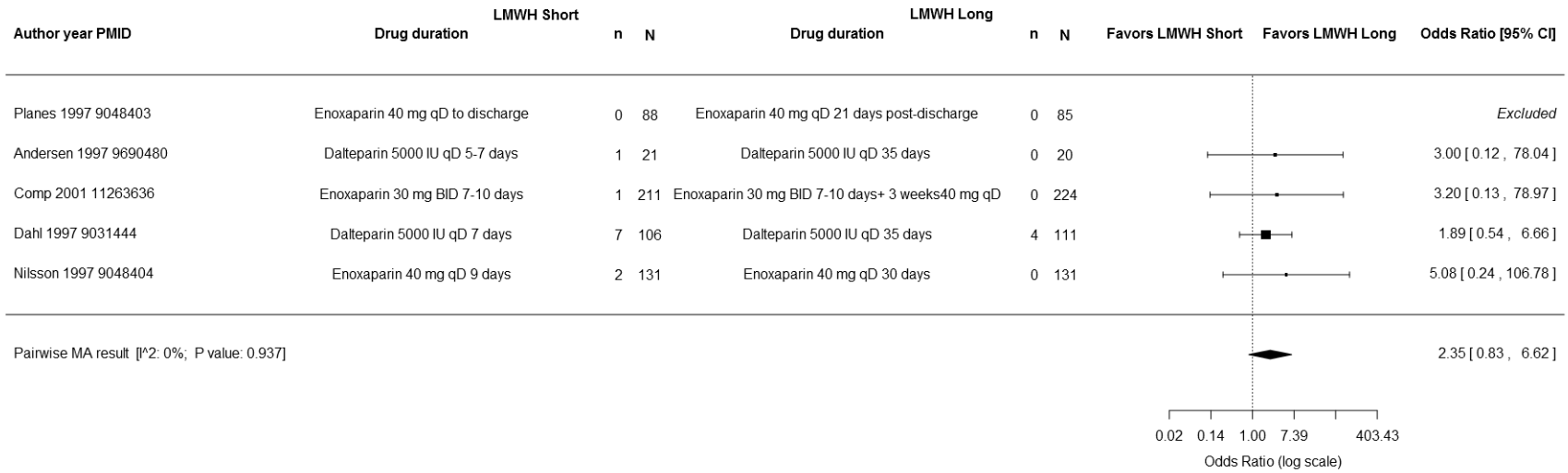
Table 9. Results summary: Total hip replacement, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
FXaI, short vs. long duration	DVT, Total	1	40	No estimate			1 RCT
LMWH, short vs. long duration	VTE, Symptomatic	2	697	**3.46** (**1.94, 6.17**)	**5.33** (**1.14, 24.8**)		
	PE, Total	*5 (MA)*	*1128*	*2.35 (0.83, 6.62)*			1 RCT
	PE, Fatal	4	1087	3.17 (0.13, 78.7)			3 RCTs
	DVT, Total	*6 (MA)*	*1308*	***2.87 (2.08, 3.96)***			
	DVT, Symptomatic	3	521	0.53 (0.15, 1.81)	0.95 (0.06, 16.3)	4.20 (0.87, 20.2)	
	DVT, Proximal	*5 (MA)*	*1300*	***2.94 (1.62, 5.33)***			
	Bleeding, Major	3	895	3.00 (0.12, 74.3)			2 RCTs
	Bleeding, Fatal	4	1135	No estimate			4 RCTs
	Mortality, 30 day or in-hospital	3	873	1.02 (0.06, 16.5)			2 RCTs
	Return to OR, bleeding or infection	1	41	5.26 (0.24, 117)			
VKA, short vs. long duration	VTE, Symptomatic	1	360	3.25 (0.87, 12.2)			
	PE, Total	1	360	3.15 (0.13, 77.9)			
	PE, Fatal	1	360	No estimate			1 RCT
	DVT, Total	1	360	2.87 (0.75, 11.0)			
	DVT, Symptomatic	1	360	1.58 (0.26, 9.56)			
	DVT, Proximal	1	360	3.17 (0.33, 30.8)			
	Bleeding, Major	1	360	0.35 (0.01, 8.56)			
	Bleeding, Fatal	1	360	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, VKA = vitamin K antagonist, Short vs. Long = short therapeutic duration versus long duration.

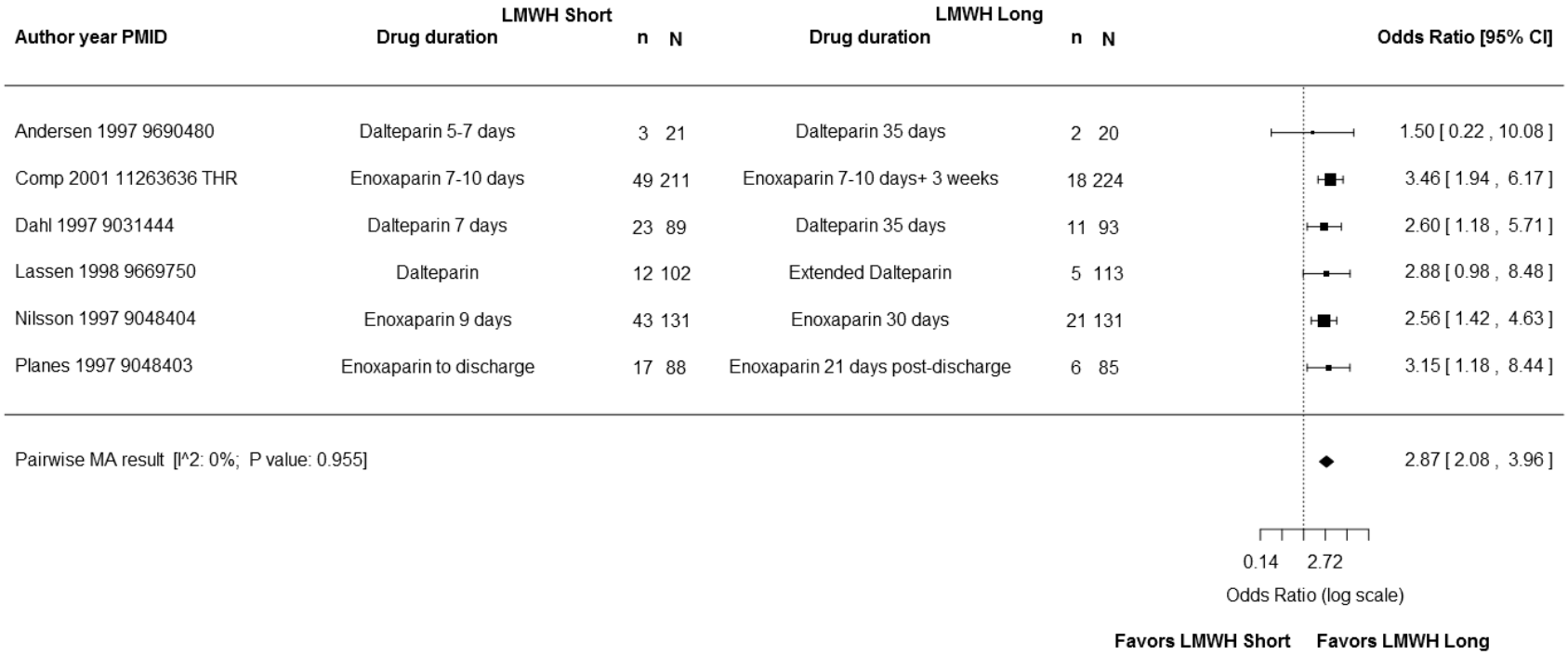
* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for LMWH, OR = 3.46 favors long duration).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Figure 35. Forest plot: Total hip replacement, total pulmonary embolism, LMWH, short versus long duration



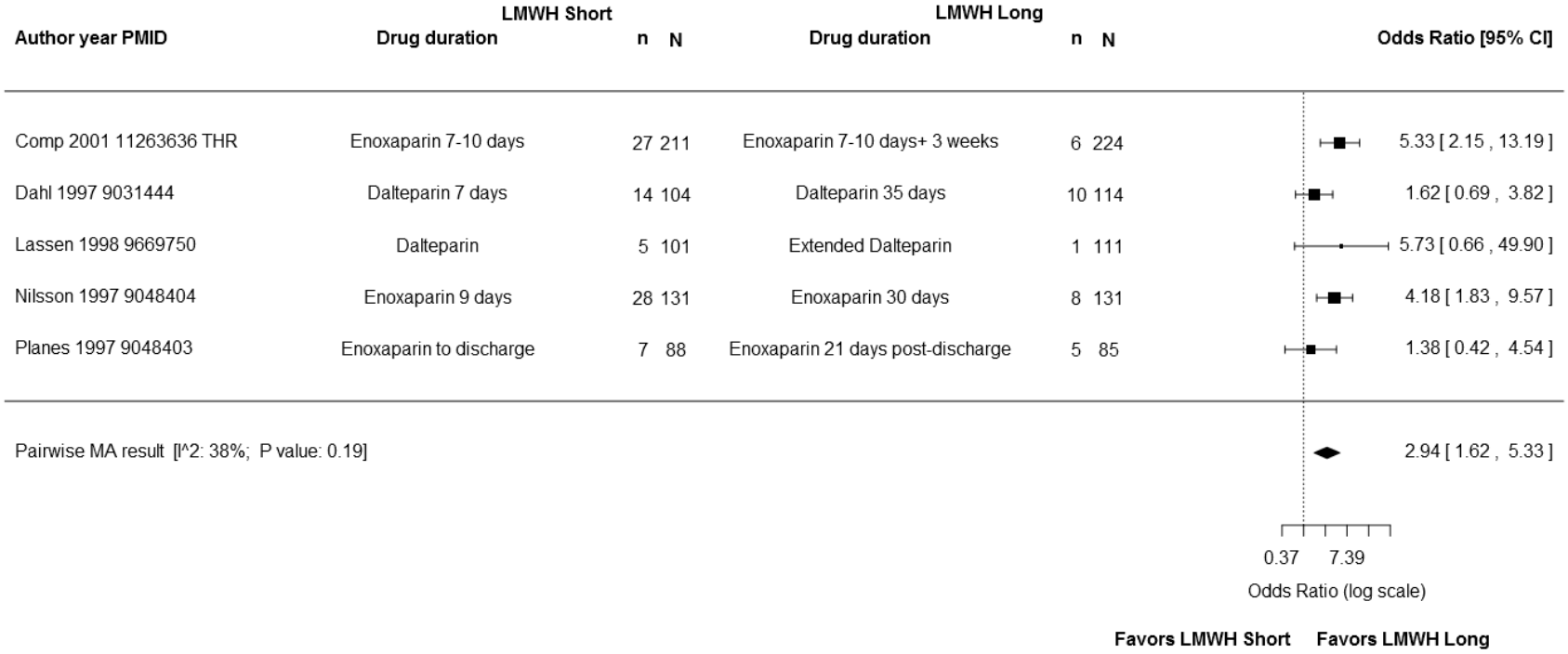
Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: LMWH = low molecular weight heparin, PE = pulmonary embolism, PMID = PubMed identifier.

Figure 36. Forest plot: Total hip replacement, total deep vein thrombosis, LMWH, short versus long duration



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Figure 37. Forest plot: Total hip replacement, proximal deep vein thrombosis, LMWH, short versus long duration



Forest plot of randomized controlled trials with calculated odds ratio and 95% confidence interval (CI) based on numbers of events (n) and sample sizes (N), with random effects model summary estimate (Pairwise meta-analysis [MA] result). I^2 = percentage of total variation across studies due to heterogeneity; P value = chi-square P value for heterogeneity.
Other abbreviations: DVT = deep vein thrombosis, LMWH = low molecular weight heparin, PMID = PubMed identifier.

Key Question 3 (Duration): Total Knee Replacement

The results summary table (Table 10) includes results for reported comparisons and outcomes from TKR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. As noted, NRCS are summarized in Appendix Table F5.

Key Question 3 (Duration, TKR): LMWH

One RCT (N=438) compared enoxaparin of short versus long therapeutic durations.[128] The study found no significant difference in symptomatic VTE, total PE, total DVT, proximal DVT, and major bleeding, and reported no fatal PE, no fatal bleeding, and no 30-day mortality. The study did not report on adherence.

Key Question 3 (Duration): Hip Fracture (HFx) Surgery

The results summary table (Table 11) is also presented at the end of the Key Question 3 section. It includes results for reported comparisons and outcomes from HFx surgery RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. As noted, NRCS are summarized in Appendix Table F6.

Key Question 3 (Duration, HFx): FXaI

One RCT (N=656) compared fondaparinux for short and long therapeutic durations.[135] The study found significantly more frequent symptomatic VTE (OR 9.11, 95% CI 1.15 to 72.3), total DVT (OR 35.1, 95% CI 10.9 to 113.6), and proximal DVT (OR 20.5, 95% 4.86 to 86.4) in the short duration group. No significant differences were found for total PE, fatal PE, and symptomatic DVT.

The study found no significant difference in major bleeding, fatal bleeding, bleeding leading to reoperation, and bleeding at surgical site or joint, and reported no bleeding leading to infection. The study did not report on adherence.

Key Question 3 (Duration, HFx): LMWH

One RCT (N=469) compared semuloparin of short versus long durations.[136] The study found significantly fewer total DVT and proximal DVT in the long duration group. No significant difference was found in fatal PE, major bleeding, 30-day mortality, and serious adverse events. The study did not report on adherence.

Table 10. Results summary: Total knee replacement, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
LMWH, short vs. long duration	VTE, Symptomatic	1	438	1.24 (0.77, 2.00)			
	PE, Total	1	438	4.95 (0.24, 104)			
	PE, Fatal	1	438	No estimate			1 RCT
	DVT, Total	1	438	1.24 (0.77, 2.00)			
	DVT, Proximal	1	438	1.93 (0.84, 4.42)			
	Bleeding, Major	1	438	2.96 (0.12, 73.0)			
	Bleeding, Fatal	1	438	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	438	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Short vs. Long = short therapeutic duration versus long duration.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for VTE, Symptomatic, OR = 1.24 favors long duration).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Table 11. Results summary: Hip fracture surgery, duration comparisons

Comparison	Outcome	Studies, N	Patients, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
FXaI, short vs. long duration	VTE, Symptomatic	1	656	**9.11** (**1.15, 72.3**)			
	PE, Total	1	656	6.98 (0.36, 136)			
	PE, Fatal	1	656	2.97 (0.12, 73.2)			
	DVT, Total	1	426	**35.1** (**10.9, 114**)			
	DVT, Symptomatic	1	656	6.02 (0.72, 50.3)			
	DVT, Proximal	1	443	**20.5** (**4.86, 86.4**)			
	Bleeding, Major	1	656	0.24 (0.05, 1.16)			
	Bleeding, Fatal	1	656	1.33 (0.46, 3.89)			
	Bleeding, Leading to reoperation	1	656	0.99 (0.14, 7.10)			
	Bleeding, Surgical site/joint	1	656	0.08 (<0.01, 1.34)			
	Bleeding, Leading to infection	1	656	No estimate			1 RCT
LMWH, short vs. long duration	PE, Fatal	1	469	5.99 (0.24, 148)			
	DVT, Total	1	330	**5.03** (**2.16, 11.7**)			
	DVT, Proximal	1	394	**6.23** (**1.94, 20.0**)			
	Bleeding, Major	1	469	0.66 (0.03, 16.3)			
	Mortality, 30 day or in-hospital (AE)	1	469	10.1 (0.48, 211)			
	Serious adverse event (study-defined)	1	469	2.38 (0.79, 7.21)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, Short vs. Long = short therapeutic duration versus long duration.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for FXaI, OR = 9.11 favors long duration).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Key Question 4: Comparison of Single Versus Combination Thromboprophylaxis Intervention Classes

Note that network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5.

Key Question 4: Total Hip Replacement

The results summary table (Table 12) includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section.

Key Question 4 (THR): Antiplatelet Drug Versus Combination Antiplatelet Drug and Mechanical Device

One RCT compared an antiplatelet drug alone versus combination antiplatelet drug and mechanical device.[137] The study found no significant difference in total PEs and no occurrences of fatal PE. The study also found no significant difference in proximal DVTs.

The study reported no episodes of fatal bleeding and found no significant difference in 30-day mortality between arms.

The study did not evaluate adherence.

Key Question 4 (THR): LMWH Versus Combination LMWH and Antiplatelet Drug

One RCT compared LMWH to a combination of LMWH and an antiplatelet drug.[138] The study found no significant differences in VTE outcomes, including symptomatic VTE, symptomatic PE, symptomatic DVT, and proximal DVT. No patient had a fatal PE.

The study also found no significant difference in major bleeding, surgical site bleeding, or wound infection.

The study did not evaluate adherence.

Key Question 4 (THR): LMWH Versus Combination LMWH and DTI

One RCT compared LMWH to a combination of LMWH and DTI.[45] The study reported only no significant difference in total DVT. Adverse events and adherence were not reported.

Key Question 4 (THR): LMWH Versus Combination LMWH and FXaI

The same RCT compared LMWH to a combination of LMWH and FXaI.[45] The study reported only that there was no significant difference in total DVT. Adverse events and adherence were not reported.

Key Question 4 (THR): LMWH Versus Combination LMWH and Mechanical Device

Three RCTs compared LMWH to a combination of LMWH and a mechanical device.[139-141] One of the studies reported no PEs. One study found significantly decreased risk of total DVT in the combined intervention group (OR=22.7, 95% CI 1.27 to 407), while the other two studies

found no significant difference between groups. Regarding proximal DVT, one study had no such events and the other found no significant difference between arms.

One study reported no fatal bleeding or 30-day mortality. Neither study evaluated adherence.

Key Question 4 (THR): Mechanical Device Versus Combination Mechanical Device and Antiplatelet Drug

One RCT compared a mechanical device alone versus a combination of a mechanical device and an antiplatelet drug.[44] The study found no significant difference in total PE or proximal DVTs. Adverse events and adherence were not reported.

Key Question 4 (THR): Mechanical Device Versus Combination Mechanical Device and Antiplatelet Drug and UFH

One RCT compared a mechanical device alone versus a combination of a mechanical device, an antiplatelet drug, and UFH.[142] The study found no occurrences of DVT (total, symptomatic, or proximal), fatal bleeding, or 30-day mortality. The study did not report on adherence.

Key Question 4 (THR): Mechanical Device Versus Combination Mechanical Device and VKA

One RCT compared a mechanical device versus a combination of a mechanical device and a VKA.[44] The study had no PEs and found no significant difference in proximal DVTs. Adverse events and adherence were not reported.

Key Question 4 (THR): UFH Versus Combination UFH and LMWH

One RCT compared UFH alone versus combination UFH and LMWH.[143] The study reported only no significant difference in total DVT. Adverse events and adherence were not reported.

Key Question 4 (THR): Combination UFH and Antiplatelet Drug Versus Combination UFH and Antiplatelet Drug and Mechanical Device

One RCT compared combination UFH and an antiplatelet drug with the further addition of a mechanical device.[142] The study found no significant differences in total DVT, symptomatic DVT, and proximal DVT.

The study reported no fatal bleeding or 30-day mortality. It did not evaluate adherence.

Key Question 4: Total Knee Replacement

The results summary table (Table 13) includes results for all reported comparisons and outcomes from THR RCTs. The reader should refer to this table for each results section summary even though the table is not repeatedly cited in each section. Where data are summarized only in appendix tables or are summarized in figures, these are cited.

Key Question 4 (TKR): Antiplatelet Drug Versus Combination Antiplatelet Drug and Mechanical Device

One RCT compared an antiplatelet drug alone versus a combination of an antiplatelet drug and a mechanical device.[144] The study found significantly more total DVTs in the antiplatelet drug alone arm, but no significant difference in proximal DVT (although still favoring the combination arm).

The study had no episodes of major bleeding and did not report on adherence.

Key Question 4 (TKR): FXaI Versus Combination FXaI and Mechanical Device

One RCT (N=120) compared FXaI with combined FXaI and mechanical device. It found no significant differences in total VTE, symptomatic VTE, total DVT, symptomatic DVT, major bleeding, or surgical site or joint bleeding between the two comparison groups. The study reported no PE, proximal DVT, or fatal bleeding in either groups.[108]

Key Question 4 (TKR): Combination LMWH Drug and Mechanical Device Versus Combination Antiplatelet and Mechanical Device

One RCT (N=275) compared combination of LMWH and mechanical device versus combination of antiplatelet and mechanical device. No significant differences were found in total DVT, proximal DVT, or total PE between the two combined interventions. The study reported rates of good adherence (to drugs only) higher than 90% in both groups.[90]

Key Question 4 (TKR): LMWH Versus Combination LMWH and FEI

One RCT compared LMWH alone versus combination LMWH and FEI.[145] The study found that significantly more patients in the LMWH alone arm had total DVT. The studies reported no PE or episodes of symptomatic DVT. There was no significant difference in proximal DVT.

The study had no episodes of major bleeding and did not report on adherence.

Key Question 4 (TKR): LMWH Versus Combination LMWH and Mechanical Device

Four RCTs compared LMWH and combination LMWH and a mechanical device;[139, 141, 146, 147] however, events were rare across the studies. One study reported no total VTE events, another found no significant difference in total PEs, while the third reported no symptomatic PEs. Total DVT was reported by three studies, one with no events and two with no significant difference between arms. Proximal DVT events also did not occur in one study.

One RCT reported no fatal bleeding events or 30-day mortality. No study reported on adherence.

Key Question 4 (TKR): UFH Versus Combination UFH and LMWH

One RCT compared UFH alone and UFH combined with LMWH.[143] No significant difference was reported in total DVTs. No adverse event or adherence data were reported.

Key Question 4: Hip Fracture Surgery

No studies compared single class and combination class interventions after HFx surgery.

Table 12. Results summary: Total hip replacement, single versus combination class comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
Antiplatelet vs. Antiplatelet+Mechanical Devices	PE, Total	1	0.96 (0.06, 15.5)			
	PE, Fatal	1	No estimate			1 RCT
	DVT, Proximal	1	15.9 (0.90, 281)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	0.32 (0.01, 7.85)			
LMWH vs. LMWH+Antiplatelet	VTE, Symptomatic	1	5.80 (0.70, 48.4)			
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	6.73 (0.35, 131)			
	DVT, Symptomatic	1	2.88 (0.30, 27.8)			
	DVT, Proximal	1	1.91 (0.17, 21.2)			
	Bleeding, Major	1	2.89 (0.12, 71.3)			
	Bleeding, Surgical site/joint	1	1.21 (0.32, 4.52)			
	Infection, Wound	1	0.80 (0.34, 1.87)			
LMWH vs. LMWH+DTI	DVT, Total	1	2.36 (0.55, 10.2)			
LMWH vs. LMWH+FXaI	DVT, Total	1	1.27 (0.35, 4.57)			
LMWH vs. LMWH+Mechanical Devices	PE, Total	1	No estimate			1 RCT
	DVT, Total	3	1.80 (0.62, 5.27)	2.25 (0.20, 25.4)	**22.7** (**1.27, 407**)	
	DVT, Proximal	2	2.74 (0.75, 10.1)			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
Mechanical Device vs. Antiplatelet+Mechanical Device	PE, Total	1	0.32 (0.01, 7.87)			
	DVT, Proximal	1	1.25 (0.44, 3.55)			
Mechanical Device vs. Mechanical Device+UFH+Antiplatelet	DVT, Total	1	No estimate			1 RCT
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	No estimate			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
Mechanical Device vs. Mechanical Device+VKA	PE, Total	1	No estimate			1 RCT
	DVT, Proximal	1	1.41 (0.47, 4.19)			

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
UFH vs. UFH+LMWH	DVT, Total	1	0.62 (0.05, 7.00)			
UFH+Antiplatelet vs. UFH+Antiplatelet+Mechanical Device	DVT, Total	1	13.7 (0.71, 262)			
	DVT, Symptomatic	1	7.93 (0.39, 162)			
	DVT, Proximal	1	13.7 (0.71, 262)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, LMWH = low molecular weight heparin, DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, UFH = unfractionated heparin, VKA = vitamin K antagonist.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Antiplatelet vs. Antiplatelet+Mechanical Devices, OR = 0.96 (marginally) favors antiplatelet).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Table 13. Results summary: Total knee replacement, single versus combination class comparisons

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
Antiplatelet vs. Antiplatelet+Mechanical Device	DVT, Total	1	**5.45** (**2.09, 14.2**)			
	DVT, Proximal	1	13.2 (0.71, 248)			
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. LMWH+FEI	PE, Total	1	No estimate			1 RCT
	DVT, Total	1	**3.19** (**1.48, 6.90**)			
	DVT, Symptomatic	1	No estimate			1 RCT
	DVT, Proximal	1	2.88 (0.29, 28.3)			
	Bleeding, Major	1	No estimate			1 RCT
LMWH vs. LMWH+Mechanical Device	VTE, Total	1	No estimate			1 RCT
	PE, Total	1	0.99 (0.06, 16.1)			
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	3	1.65 (0.51, 5.28)	2.03 (0.43, 9.44)		1 RCT
	DVT, Proximal	1	No estimate			1 RCT
	Bleeding, Fatal	1	No estimate			1 RCT
	Mortality, 30 day or in-hospital	1	No estimate			1 RCT
UFH vs. UFH+LMWH	DVT, Total	1	0.15 (0.02, 1.31)			
FXaI vs. FXaI+Mechanical Device	VTE, Total	1	0.48 (0.20, 1.13)			
	VTE, Symptomatic	1	0.30 (0.03, 2.97)			
	PE, Total	1	No estimate			1 RCT
	PE, Fatal	1	No estimate			1 RCT
	PE, Symptomatic	1	No estimate			1 RCT
	DVT, Total	1	0.48 (0.20, 1.13)			
	DVT, Symptomatic	1	0.30 (0.03, 2.97)			
	DVT, Proximal	1	No estimate			1 RCT
	Bleeding, Major	1	0.93 (0.18, 4.81)			
	Bleeding, Fatal	1	No estimate			1 RCT
	Bleeding, Surgical site/joint	1	0.93 (0.13, 6.85)			
LMWH+Mechanical Device vs. Antiplatelet+Mechanical Device	PE, Total	1	0.32 (0.01, 7.83)			
	DVT, Total	1	0.75 (0.39, 1.46)			

Comparison	Outcome	Studies, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
	DVT, Proximal	1	1.62 (0.38, 6.90)			
	Adherent/Compliant	1	0.06 (<0.01, 1.01)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, Antiplatelet = antiplatelet agent, LMWH = low molecular weight heparin, FEI = factor VIII inhibitor, UFH = unfractionated heparin.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for Antiplatelet vs. Antiplatelet+Mechanical Device, OR = 5.45 favors Antiplatelet+Mechanical Device).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Key Question 5: Network Meta-Analyses Across Classes of Thromboprophylaxis Interventions

For all three major orthopedic surgeries, network meta-analyses that included more than sparse connections could be constructed only for total DVT and major bleeding. Sensitivity analyses with informative priors, added due to network sparseness, yielded similar findings (Appendix G). Due to incomplete and selective outcome reporting by most articles, other outcomes were too sparsely populated to allow interpretable networks (networks for symptomatic DVT and total PE are provided in Appendix H). Overall, network meta-analysis findings were consistent with direct, pairwise comparisons, with the caveat that they pertain only to total DVT and major bleeding.

When interpreting the findings of the network meta-analyses, it is important to recognize that the exact ranking of interventions is susceptible to change with the addition of more studies. Interventions with relatively sparse data are likely to have imprecise rankings (i.e., to have flat rank graphs with similar likelihood across a range of ranks); see rank graphs for each network. Furthermore, while the pairwise comparisons with a network yield summary estimates and confidence intervals, the ranking of interventions is not supported by evaluations of statistical significance. Conclusions on total DVT may not translate to other, clinically significant, VTE outcomes, as suggested by the lack of correlation across studies between rates of total DVT and total PE.

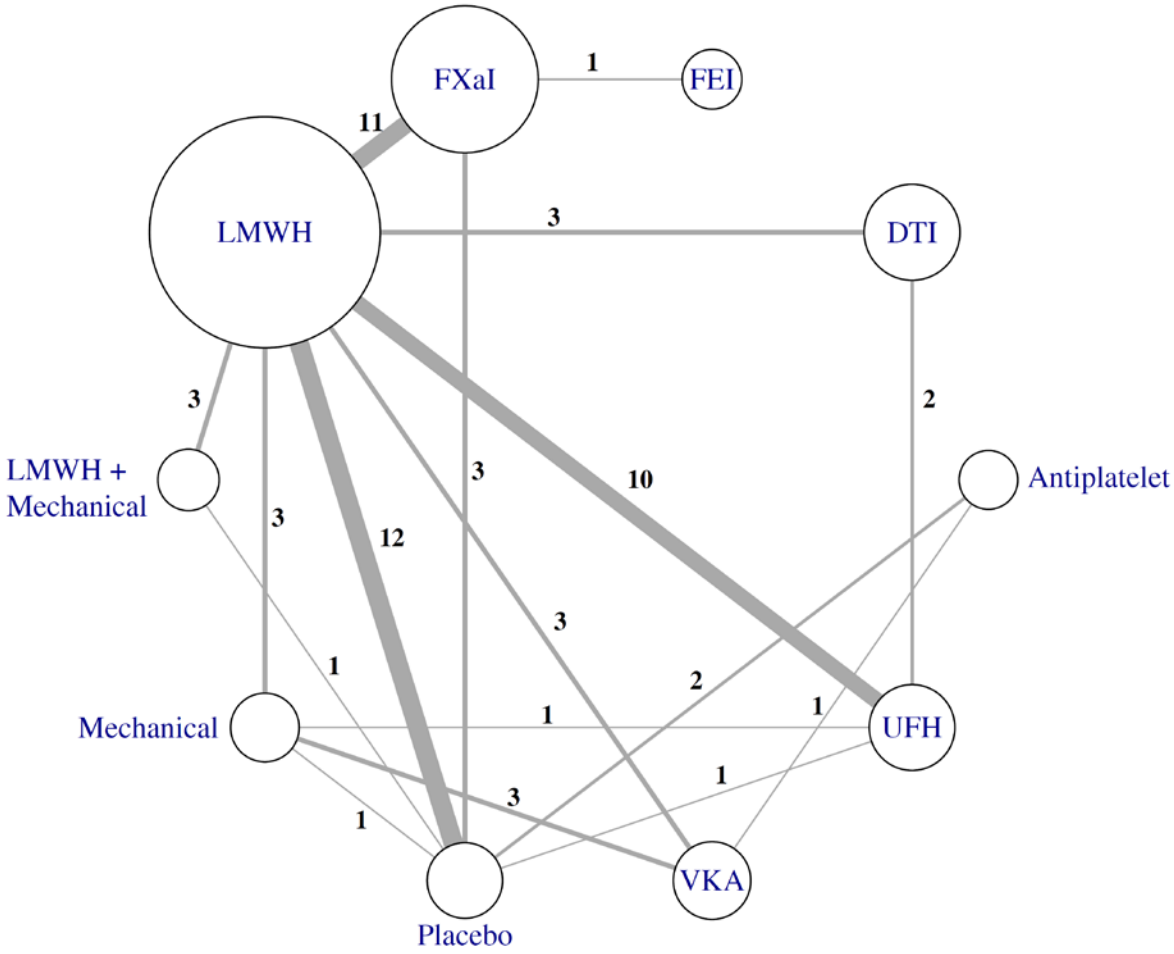
Key Question 5: Total Hip Replacement

Key Question 5 (THR): Deep Vein Thrombosis, Total

Comparison of Classes

There were 53 RCTs that evaluated interventions in at least two classes and reported total DVT after THR.[24, 43, 46-50, 52, 54-56, 58, 60-64, 66-76, 78, 80-86, 120, 139-141, 148-159] The RCTs compared pairs of intervention classes (47 RCTs) or triplets of intervention classes (3 RCTs). Across this study set, 10 classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. Figure 38 illustrates the topology of the network. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (9 RCTs), UFH (10 RCTs) and placebo (12 RCTs). Antiplatelet drug was directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Figure 38. Network of comparison of intervention classes for total deep vein thrombosis in total hip replacement



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after total hip replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.1 shows the network meta-analysis pairwise results for all combinations of interventions classes. The statistically significant differences between classes are highlighted here.

- **FXaI** had a lower odds of DVT compared with
  - *LMWH* (OR=0.601; 95% CrI 0.409 to 0.900)
  - *UFH* (OR=0.387; 95% CrI 0.224 to 0.669)
  - *VKA* (OR=0.404; 95% CrI 0.215 to 0.78)
- **DTI** had a lower odds of DVT compared with
  - *UFH* (OR=0.437; 95% CrI 0.248 to 0.750)
  - *VKA* (OR=0.455; 95% CrI 0.222 to 0.941)

- **LMWH** had a lower odds of DVT compared with
  - *UFH* (OR=0.644; 95% CrI 0.434 to 0.934)
- **Mechanical Devices** had lower odds of DVT versus
  - *UFH* (OR=0.522; 95% CrI 0.270 to 0.962)
  - *VKA* (OR=0.544; 95% CrI 0.299 to 0.968)
- The **combination of LMWH plus mechanical device** had lower odds of DVT compared with
  - *Antiplatelet drug (aspirin)* (OR=0.242; 95% CrI 0.056 to 0.965)
  - *DTI* (OR=0.289; 95% CrI 0.080 to 0.927)
  - *FXaI* (OR=0.327; 95% CrI 0.094 to 0.999)
  - *LMWH* (OR=0.196; 95% CrI 0.061 to 0.566)
  - *Mechanical devices* (OR=0.241; 95% CrI 0.069 to 0.802)
  - *UFH* (OR=0.126; 95% CrI 0.037 to 0.386)
  - *VKA* (OR=0.132; 95% CrI 0.037 to 0.422)

Summary

Overall, the combination of LMWH plus mechanical device had the highest probability of being among the top three intervention classes (99%) to prevent DVT in patients undergoing THR, followed by FXaI (64%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (86%), and VKA (80%) (Table 14). The distribution of intervention ranks is provided in Figure 39.

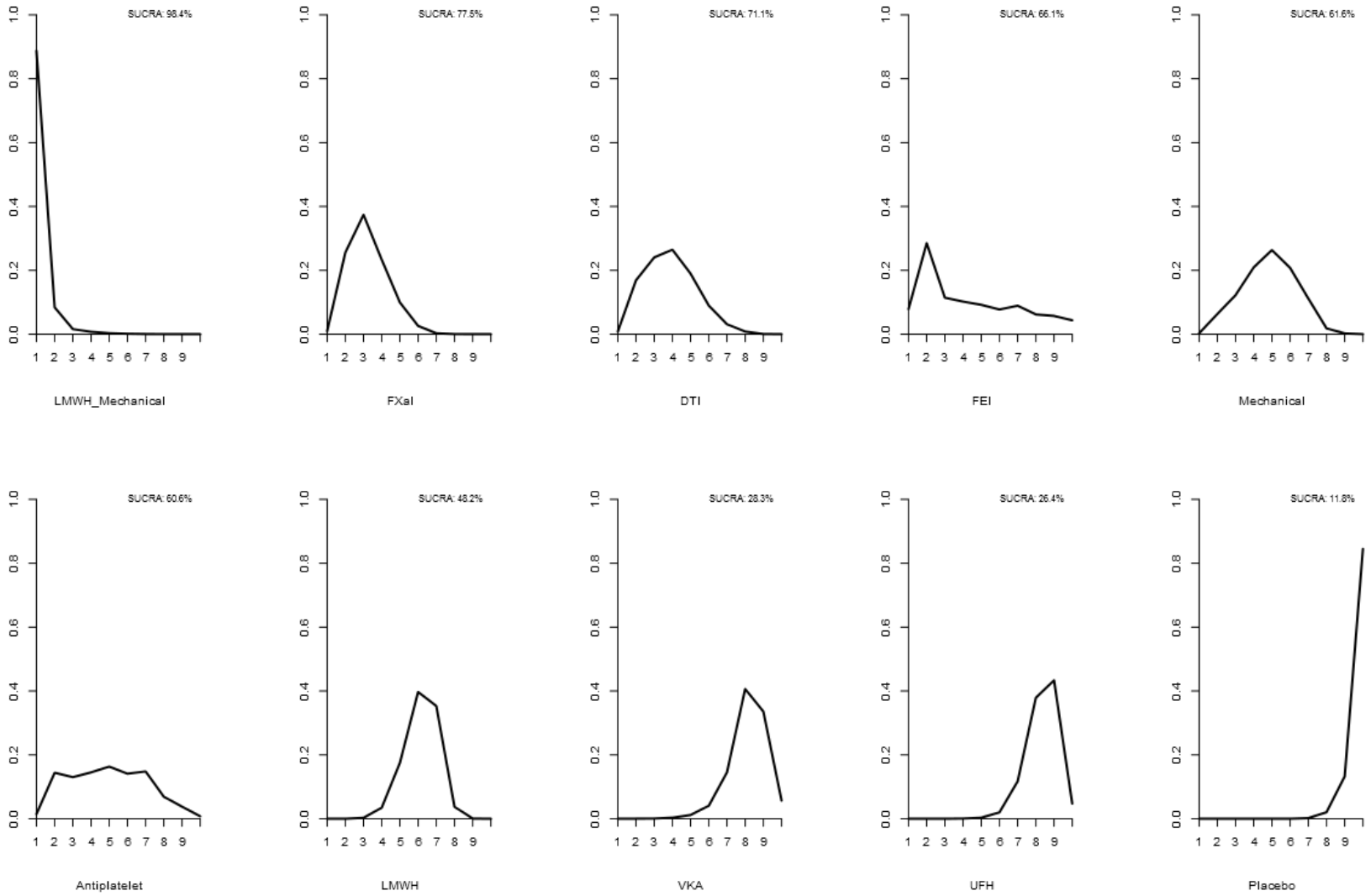
However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drug [aspirin], FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, compared with mechanical devices, LMWH, VKA, and UFH.

Table 14. Class ranking: Total hip replacement, intervention class comparisons to prevent deep vein thrombosis

	Top 3 Ranks	Bottom 3 Ranks
LMWH+Mechanical Device	99%	0%
FXaI	64%	0%
DTI	42%	1%
FEI	48%	16%
Mechanical Device	19%	2%
Antiplatelet Drug	29%	11%
LMWH	0%	4%
VKA	0%	80%
UFH	0%	86%
Placebo	0%	>99%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 39. Network meta-analysis ranks of intervention classes to prevent total deep vein thrombosis in total hip replacement

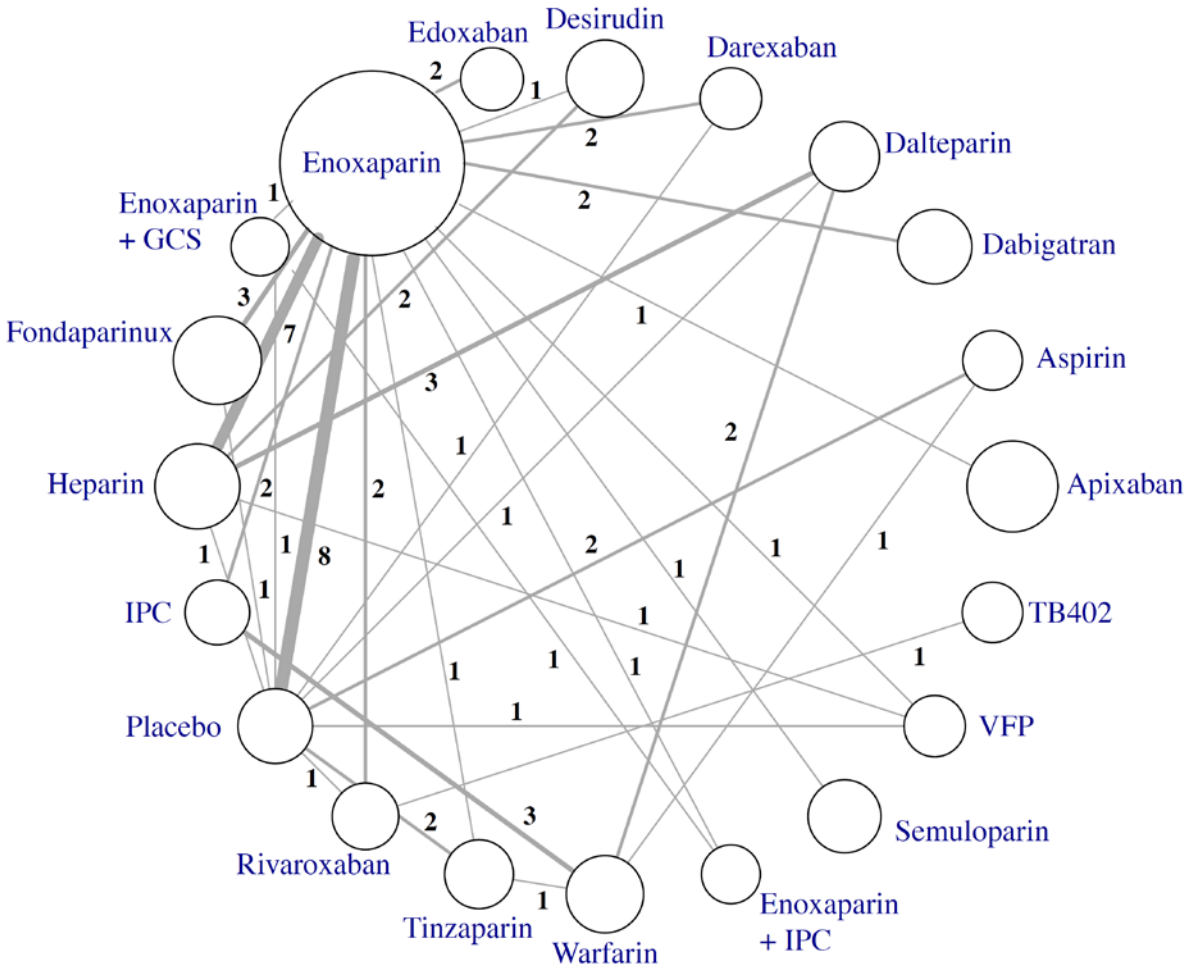


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 54 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included.[141] Hence, there were 53RCTs in the network meta-analysis.[24, 43, 46-50, 52, 54-56, 58, 60-63, 66-76, 78, 80-86, 114, 115, 117, 120, 139, 140, 148-151, 153-159] These RCTs compared pairs of interventions (49 RCTs) or triplets of interventions (4 RCTs). Across this study set, 20 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, VFP, warfarin, placebo). Of the 190 possible pairwise comparisons, 33 are covered by direct study comparisons. Figure 40 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with UFH (7 RCTs) and placebo (7 RCTs). Dalteparin was directly compared with UFH, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was also directly compared with placebo; TB402 was directly compared with rivaroxaban only.

Figure 40. Network of comparison of specific interventions for total deep vein thrombosis in total hip replacement



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after total hip replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: GCS = graduated compression stocking, IPC = intermittent pneumatic compression, VFP = venous foot pump.

Appendix Table F7.2 shows the network meta-analysis pairwise results for all combinations of interventions. The statistically significant differences between active interventions are highlighted here.

- The combination of **enoxaparin plus IPC** had statistically significant lower odds of DVT compared with 13 active interventions
- **Apixaban** had a lower odds of DVT compared with
    - *enoxaparin* (OR=0.306; 95% CrI 0.114 to 0.813)
    - *UFH* (OR=0.213; 95% CrI 0.071 to 0.593)
    - *rivaroxaban* (OR=0.238; 95% CrI 0.067 to 0.863)

    - *tinzaparin* (OR=0.208; 95% CrI 0.063 to 0.625)
    - *warfarin* (OR=0.177; 95% CrI 0.053 to 0.552)
- **Desirudin** had a lower odds of DVT compared with
    - *UFH* (OR=0.390; 95% CrI 0.212 to 0.678)
    - *tinzaparin* (OR=0.380; 95% CrI 0.161 to 0.844)
    - *warfarin* (OR=0.324; 95% CrI 0.137 to 0.738)
- **Edoxaban** had a lower odds of DVT compared with
    - *UFH* (OR=0.264; 95% CrI 0.080 to 0.815)
    - *tinzaparin* (OR=0.256; 95% CrI 0.071 to 0.854)
    - *warfarin* (OR=0.219; 95% CrI 0.060 to 0.758)
- The combination of **enoxaparin plus GCS** had a lower odds of DVT compared with
    - *UFH* (OR=0.288; 95% CrI 0.078 to 0.991)
    - *warfarin* (OR=0.239; 95% CrI 0.059 to 0.890)
- **Fondaparinux** had a lower odds of DVT compared with
    - *UFH* (OR=0.451; 95% CrI 0.227 to 0.932)
    - *warfarin* (OR=0.376; 95%CrI 0.16 to 0.907)
- **Semuloparin** had a lower odds of DVT compared with
    - *UFH* (OR=0.375; 95% CrI 0.132 to 0.989)
    - *warfarin* (OR=0.311; 95% CrI 0.098 to 0.9238)
- **VFP** had a lower odds of DVT compared with
    - *UFH* (OR=0.483; 95% CrI 0.223 to 0.984)
    - *warfarin* (OR=0.401; 95% CrI 0.157 to 0.976)

Summary

Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions (96%) to prevent DVT after THR, followed by apixaban (67%). The interventions likely to be among the bottom three interventions were placebo (97%) and warfarin (58%) (Table 15). The distribution of intervention ranks is provided in Figure 41.

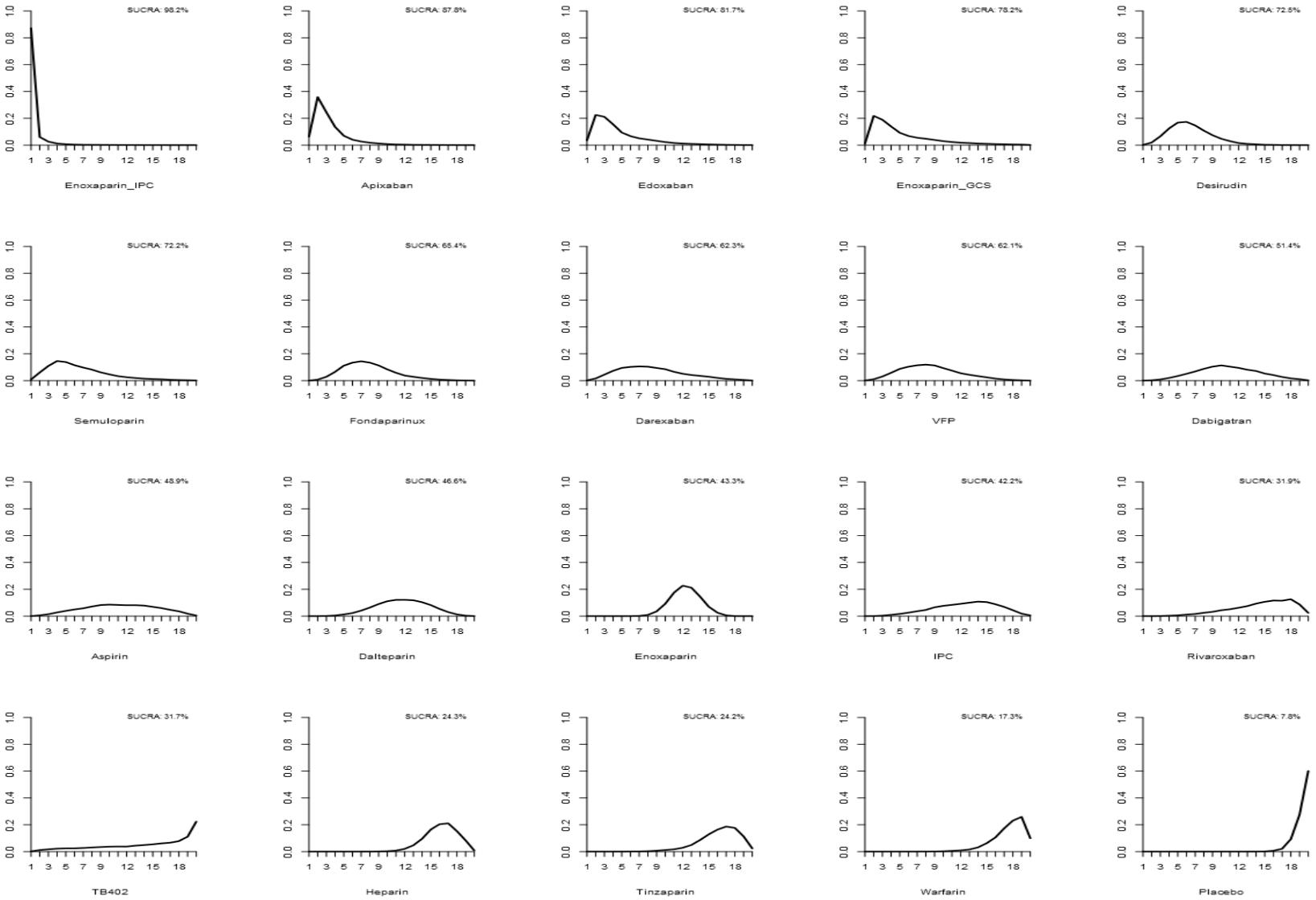
However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (most interventions), dalteparin is most effective to prevent total DVTs, compared with enoxaparin, IPC, UFH, and warfarin.

Table 15. Intervention ranking: Total hip replacement, intervention comparisons to prevent deep vein thrombosis

	Top 3 Ranks	Bottom 3 Ranks
Enoxaparin+IPC	96%	0%
Apixaban	67%	0%
Edoxaban	47%	0%
Enoxaparin+GCS	41%	1%
Desirudin	9%	0%
Semuloparin	18%	1%
Fondaparinux	4%	0%
Darexaban	7%	2%
VFP	4%	1%
Dabigatran	1%	3%
Aspirin	2%	6%
Dalteparin	0%	2%
Enoxaparin	0%	0%
IPC	1%	7%
Rivaroxaban	0%	23%
TB402	3%	42%
UFH	0%	25%
Tinzaparin	0%	31%
Warfarin	0%	58%
Placebo	0%	97%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: GCS = graduated compression stocking, IPC = intermittent pneumatic compression, UFH = unfractionated heparin, VFP = venous foot pump.

Figure 41. Network meta-analysis ranks of specific interventions to prevent total deep vein thrombosis in total hip replacement



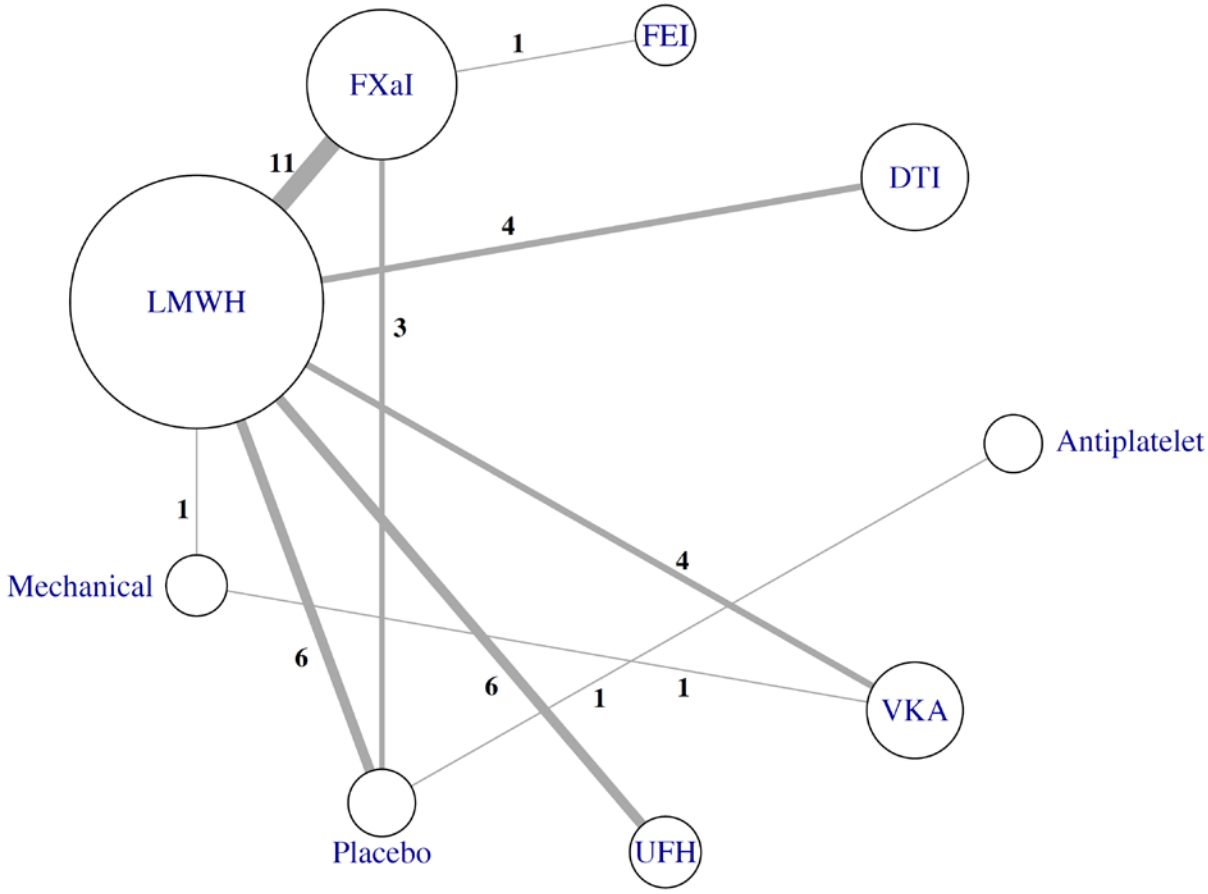
Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: GCS = graduated compression stocking, IPC = intermittent pneumatic compression, SUCRA = surface under the cumulative ranking curve, VFP = venous foot pump.

Key Question 5 (THR): Major Bleeding

Comparison of Classes

There were 32 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR.[24, 26, 48-52, 54-56, 58, 60-63, 67, 69-71, 73, 74, 76, 79-82, 86, 120, 150, 153, 157] The RCTs compared pairs of intervention classes (29 RCTs) or triplets of intervention classes (3 RCTs). Across this study set, nine classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, mechanical devices, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. Figure 42 illustrates the topology of the network. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (11 RCTs), UFH (6 RCTs), and placebo (6 RCTs). Antiplatelet drug was directly compared with placebo only; FEI was directly compared with FXaI only.

Figure 42. Network of comparison of intervention classes for major bleeding in total hip replacement



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after total hip replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.3 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with antiplatelet drug, FEI, and mechanical devices were not estimable (due to the following: there was only one RCT of antiplatelet drug versus placebo, which had zero events; there was only one RCT of FEI versus FXaI, which had rare events [5/208 vs. 0/208]; there were two RCTs of mechanical devices, which both had zero events). The statistically significant differences between classes are highlighted here.

- **VKA** had lower odds of major bleeding compared with
    - *DTI* (OR=0.393; 95% CrI 0.184 to 0.799)
    - *FXaI* (OR=0.377; 95% CrI 0.185 to 0.761)
    - *LMWH* (OR=0.509; 95% CrI 0.272 to 0.906)
    - *UFH* (OR=0.234; 95% CrI 0.099 to 0.522)

- **LMWH** had lower odds of major bleeding compared with
    - *UFH* (OR=0.459; 95% CrI 0.256 to 0.820)

Summary

Overall, the mechanical devices had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by antiplatelet drug (89%) and VKA (78%). The interventions likely to be among the bottom three interventions were FEI (>99%) and UFH (88%) (Table 16). The distribution of intervention ranks is provided in Figure 43.

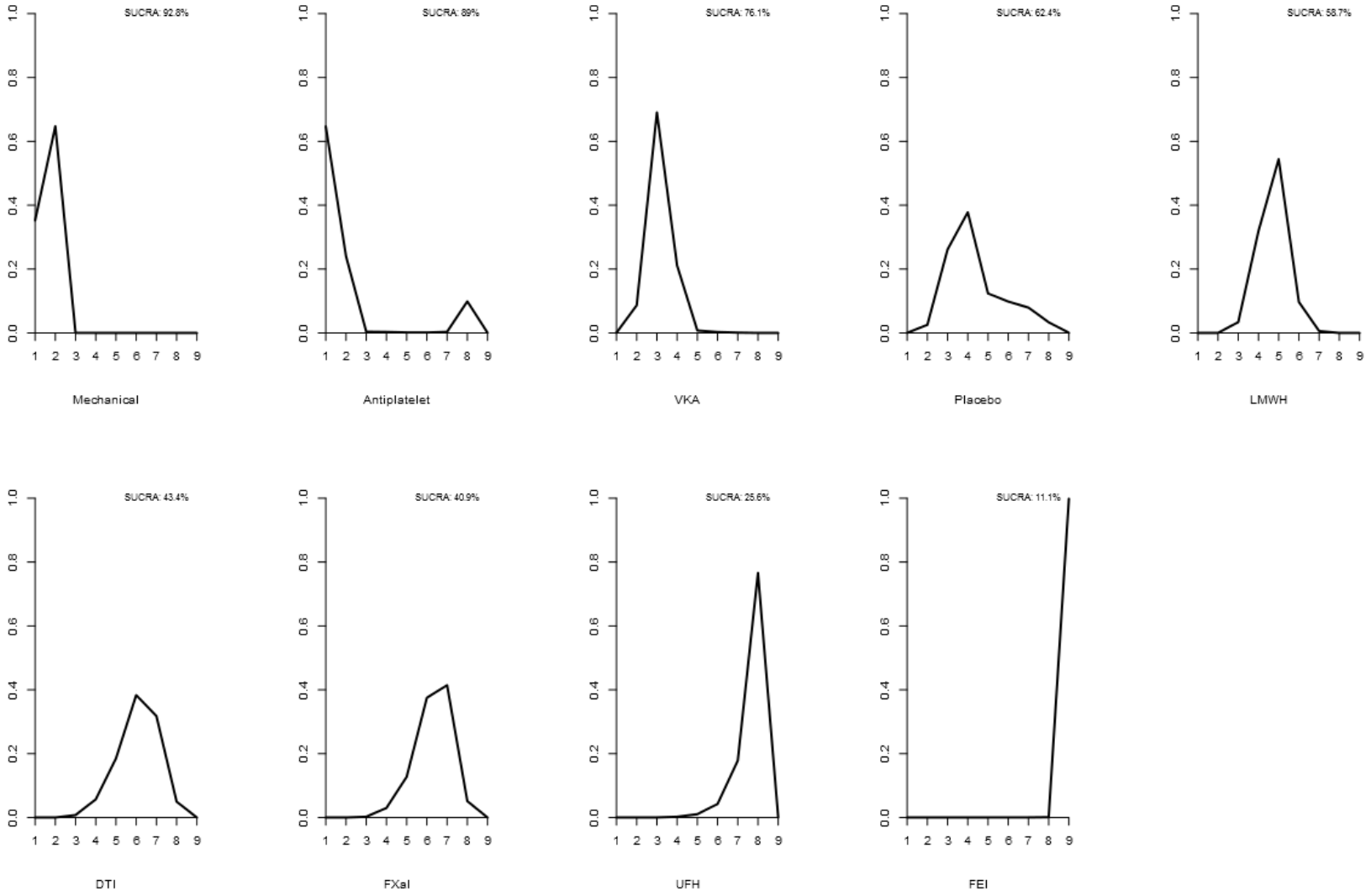
However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH was more likely to result in fewer major bleeding events than FXaI.

Table 16. Class ranking: Total hip replacement, intervention comparisons to avoid major bleeding

	Top 3 Ranks	Bottom 3 Ranks
Mechanical Devices	>99%	0%
Antiplatelet	89%	10%
VKA	78%	0%
Placebo	29%	11%
LMWH	3%	1%
DTI	1%	37%
FXaI	0%	47%
UFH	0%	94%
FEI	0%	>99%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 43. Network meta-analysis ranks of intervention classes to avoid major bleeding in total hip replacement

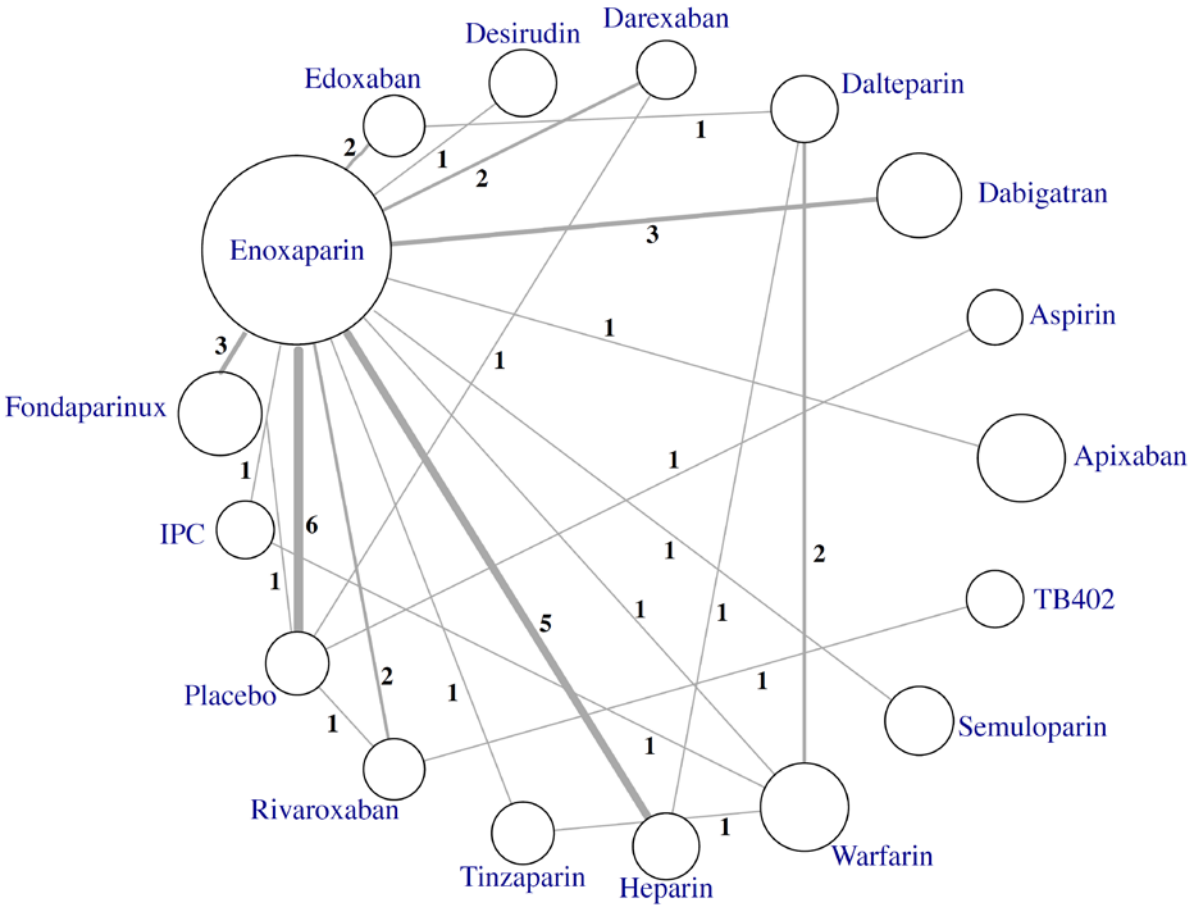


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 34 RCTs that evaluated at least two interventions and reported major bleeding after THR.[24, 26, 48-52, 54-56, 58, 60-63, 67, 69-71, 73, 74, 76, 79-82, 86, 114, 115, 120, 150, 153, 157] These studies compared pairs of interventions (31 RCTs) or triplets of interventions (3 RCTs). Across this study set, 17 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, warfarin, placebo). Of the 136 possible pairwise comparisons, 23 are covered by direct study comparisons. Figure 44 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 13 other interventions; most frequently with UFH (5 RCTs) and placebo (6 RCTs). Dalteparin was directly compared with UFH, warfarin, and edoxaban only; aspirin was directly compared with placebo only; TB402 was directly compared with rivaroxaban only.

Figure 44. Network of comparison of specific interventions for major bleeding in total hip replacement



Topology map for network meta-analysis of different interventions of thromboprophylaxis for major bleeding outcome after total hip replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: IPC = intermittent pneumatic compression.

Appendix Table F7.4 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with aspirin, IPC, and TB402 were not estimable (due to the following: there was one RCT of aspirin versus placebo which had zero events; there were two RCTs of IPC which both had zero events; there was only one RCT of TB402 versus rivaroxaban which had rare events [5/208 versus 0/208]). The statistically significant differences between active interventions are highlighted here.

- **Semuloparin** had a lower odds of major bleeding compared with
  - *dabigatran* (OR=0.179; 95% CrI 0.037 to 0.731)
  - *enoxaparin* (OR=0.264; 95% CrI 0.062 to 0.932)
  - *fondaparinux* (OR=0.164; 95% CrI 0.033 to 0.682)
  - *UFH* (OR=0.125; 95% CrI 0.023 to 0.529)

- **Warfarin** had a lower odds of major bleeding compared with
  - *dabigatran* (OR=0.242; 95% CrI 0.069 to 0.718)
  - *enoxaparin* (OR=0.356; 95% CrI 0.123 to 0.884)
  - *fondaparinux* (OR=0.221; 95% CrI 0.063 to 0.666)
  - *UFH* (OR=0.167; 95% CrI 0.049 to 0.524)
- **Enoxaparin** had a lower odds of major bleeding compared with
  - *UFH* (OR=0.471; 95% CrI 0.247 to 0.965)

Summary

Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (63%). The interventions likely to be among the bottom three interventions were TB402 (>99%) and aspirin (86%) (Table 17). The distribution of intervention ranks is provided in Figure 45.

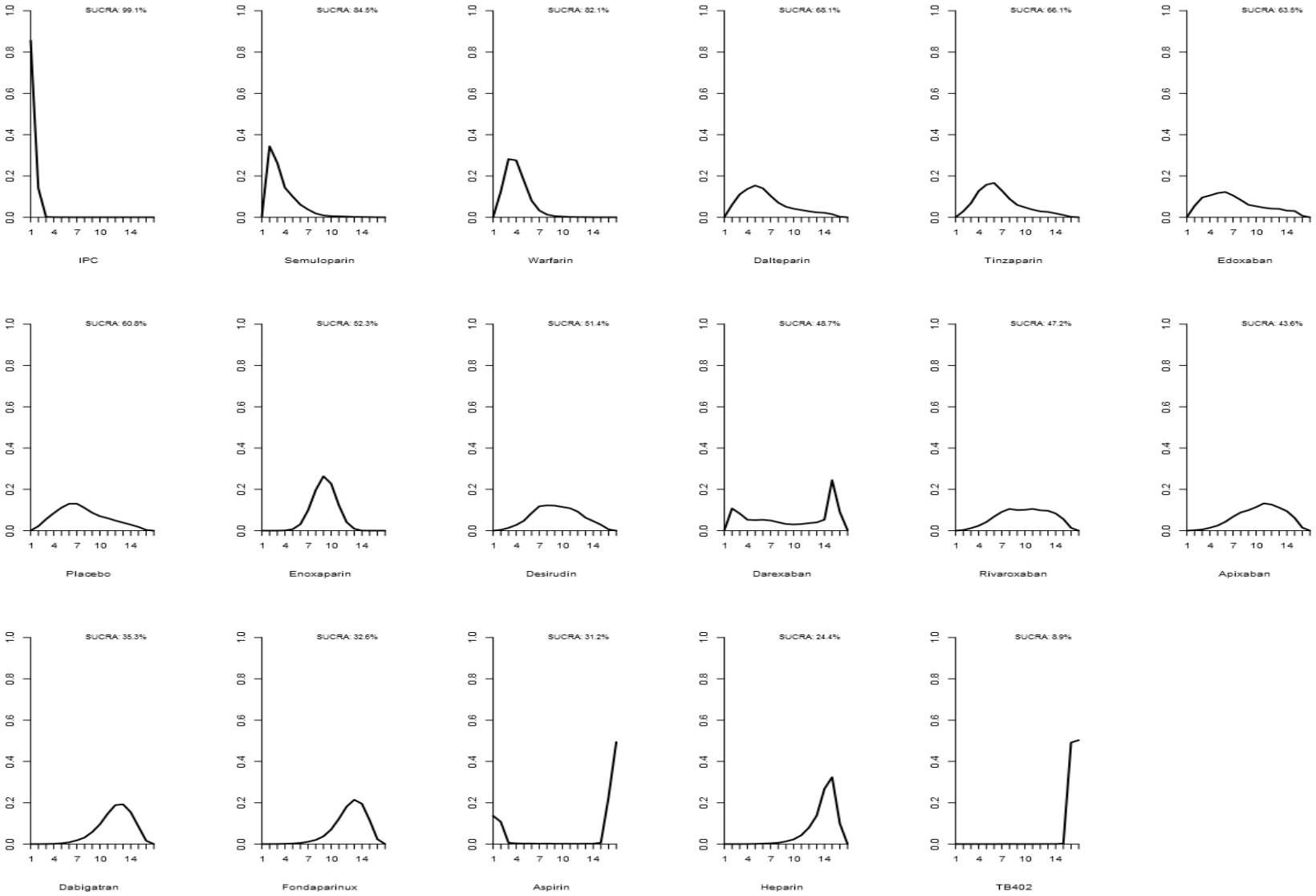
However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 17. Intervention ranking: Total hip replacement, intervention comparisons to avoid major bleeding

	Top 3 Ranks	Bottom 3 Ranks
IPC	>99%	0%
Semuloparin	63%	0%
Warfarin	44%	0%
Dalteparin	17%	2%
Tinzaparin	10%	1%
Edoxaban	17%	3%
Placebo	9%	2%
Enoxaparin	0%	0%
Darexaban	24%	30%
Desirudin	2%	3%
Rivaroxaban	1%	7%
Apixaban	1%	7%
Dabigatran	0%	8%
Fondaparinux	0%	12%
UFH	0%	41%
Aspirin	13%	86%
TB402	0%	>99%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: IPC = intermittent pneumatic compression, UFH = unfractionated heparin.

Figure 45. Network meta-analysis ranks of specific interventions to avoid major bleeding in total hip replacement



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: IPC = intermittent pneumatic compression, SUCRA = surface under the cumulative ranking curve.

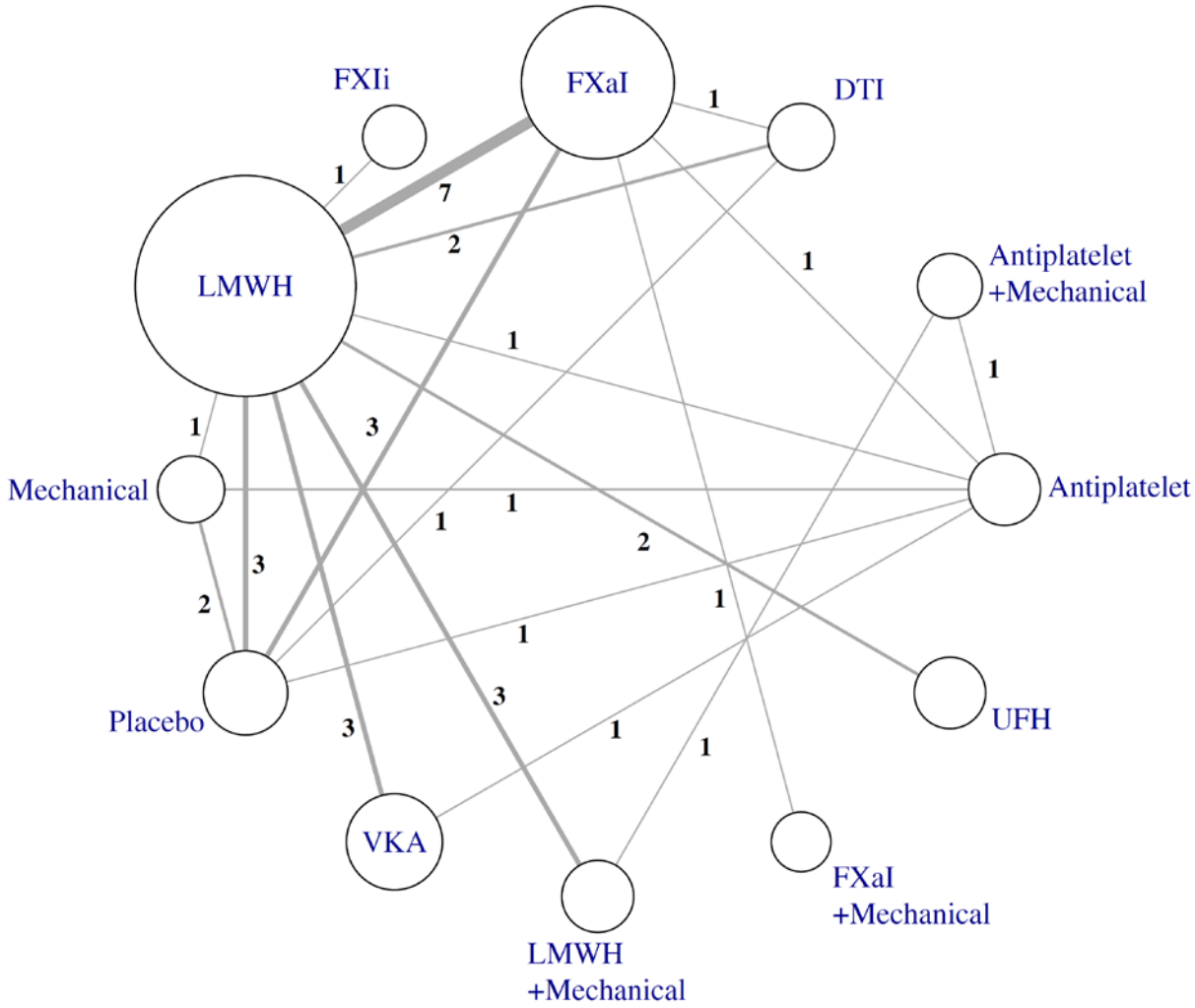
Key Question 5: Total Knee Replacement

Key Question 5 (TKR): Deep Vein Thrombosis, Total

Comparison of Classes

There were 31 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR.[43, 52, 55, 65, 80, 87-90, 95-98, 101-106, 108, 120, 126, 139, 141, 144, 147, 160-164] The RCTs compared pairs of intervention classes (28 RCTs) or triplets of intervention classes (3 RCTs). Across this study set, 12 classes were evaluated (antiplatelet drug [aspirin], antiplatelet drug plus mechanical device, DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 66 possible pairwise comparisons, 20 are covered by direct study comparisons. Figure 46 illustrates the topology of the network. LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drug (aspirin) plus mechanical device was directly compared with antiplatelet drug and LMWH plus mechanical device; the combination of FXaI plus mechanical device was directly compared with FXaI only.

Figure 46. Network of comparison of intervention classes for total deep vein thrombosis in total knee replacement



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after total knee replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.5 shows the network meta-analysis pairwise results for all combinations of interventions classes. The statistically significant differences between classes are highlighted here.

- **The combination of LMWH plus mechanical device** had a lower odds of DVT versus
  - *antiplatelet drug* (OR=0.285; 95% CrI 0.093 to 0.807)
  - *LMWH* (OR=0.417; 95% CrI 0.188 to 0.920)
  - *mechanical devices* (OR=0.393; 95% CrI 0.161 to 0.977)
  - *UFH* (OR=0.281; 95% CrI 0.118 to 0.686)

    - *VKA* (OR=0.229; 95% CrI 0.101 to 0.530)
- **FXaI** had a lower odds of DVT compared with
    - *antiplatelet drug* (OR=0.231; 95% CrI 0.140 to 0.370)
    - *LMWH* (OR=0.473; 95% CrI 0.370 to 0.587)
    - *mechanical devices* (OR=0.446; 95% CrI 0.261 to 0.747)
    - *UFH* (OR=0.320; 95% CrI 0.197 to 0.504)
    - *VKA* (OR=0.261; 95% CrI 0.18 to 0.361)
- **DTI** had a lower odds of DVT compared with
    - *antiplatelet drug* (OR=0.276; 95% CrI 0.138 to 0.534)
    - *LMWH* (OR=0.568; 95% CrI 0.330 to 0.938)
    - *UFH* (OR=0.386; 95% CrI 0.194 to 0.728)
    - *VKA* (OR=0.312; 95% CrI 0.170 to 0.549)
- **The combination of antiplatelet drug plus mechanical devices** had a lower odds of DVT compared with
    - *antiplatelet drug* (OR=0.234; 95% CrI 0.105 to 0.506)
    - *UFH* (OR=0.326; 95% CrI 0.128 to 0.800)
    - *VKA* (OR=0.263; 95% CrI 0.112 to 0.612)
- **FXIi** had a lower odds of DVT compared with
    - *antiplatelet drug* (OR=0.383; 95% CrI 0.167 to 0.877)
    - *VKA* (OR=0.435; 95% CrI 0.206 to 0.909)
- **LMWH** had a lower odds of DVT compared with
    - *antiplatelet drug* (OR=0.488; 95% CrI 0.313 to 0.752)
    - *VKA* (OR=0.553; 95% CrI 0.421 to 0.709)
- **Mechanical devices** had lower odds of DVT versus
    - *antiplatelet drug* (OR=0.513; 95% CrI 0.298 to 0.890)
    - *VKA* (OR=0.584; 95% CrI 0.341 to 0.987)

Summary

Overall, FXaI had the highest probability of being among the top three intervention classes (84%) to prevent DVT after TKR, followed closely by the combination of LMWH plus mechanical device (81%), then the combination of antiplatelet drug (aspirin) plus mechanical device (66%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drug (86%), and VKA (76%) (Table 18). The distribution of intervention ranks is provided in Figure 47.

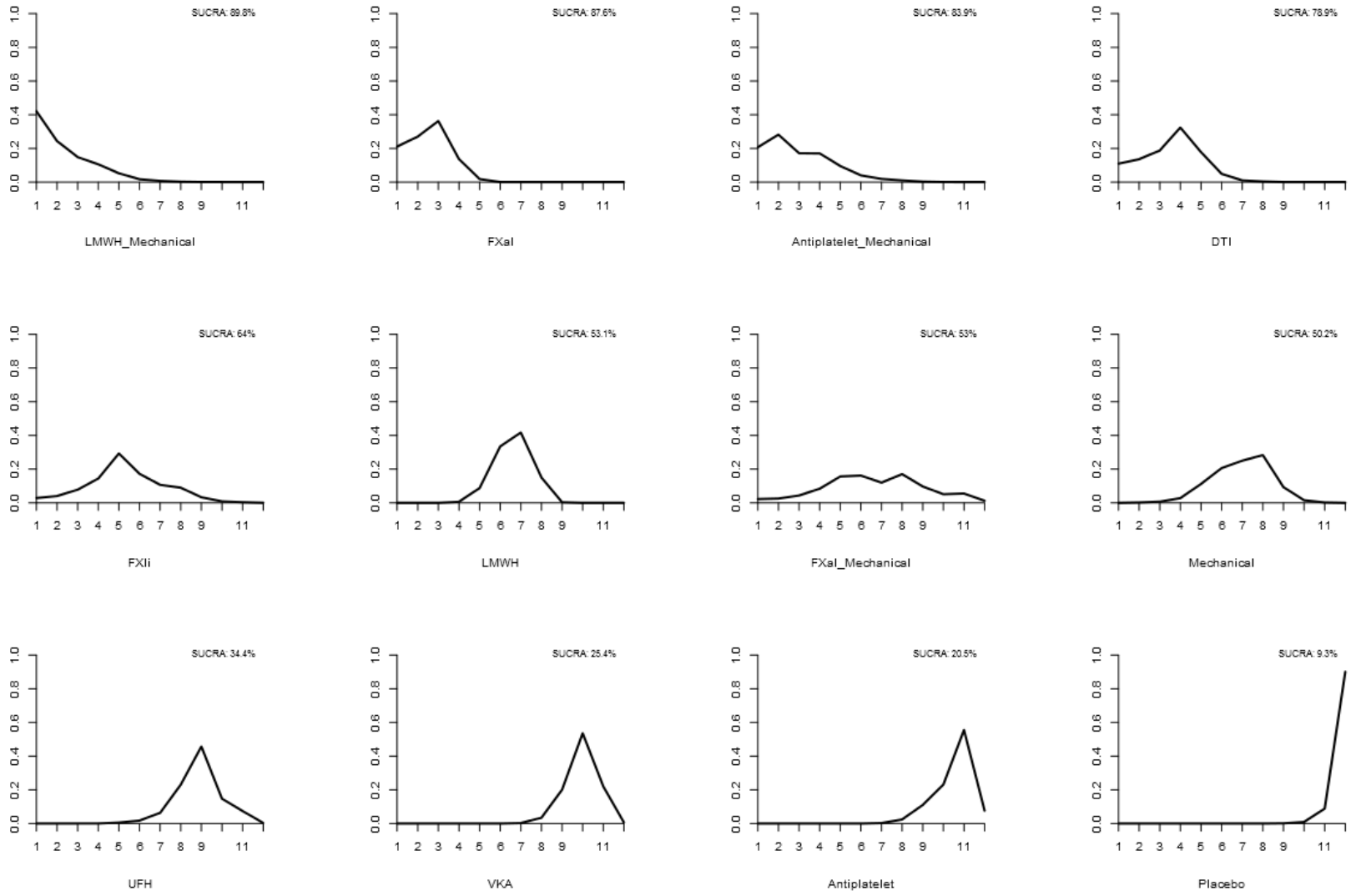
However, except for LMWH and FXaI (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. FXaI is more effective to prevent total DVTs than LMWH.

Table 18. Class ranking: Total knee replacement, intervention class comparisons to prevent deep vein thrombosis

	Top 3 Ranks	Bottom 3 Ranks
LMWH+Mechanical Device	81%	0%
FXaI	84%	0%
Antiplatelet+Mechanical Device	66%	0%
DTI	43%	0%
FXIi	15%	1%
LMWH	0%	0%
FXaI+Mechanical Device	9%	12%
Mechanical Devices	1%	2%
UFH	0%	23%
VKA	0%	76%
Antiplatelet	0%	86%
Placebo	0%	100%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 47. Network meta-analysis ranks of intervention classes to prevent total deep vein thrombosis in total knee replacement

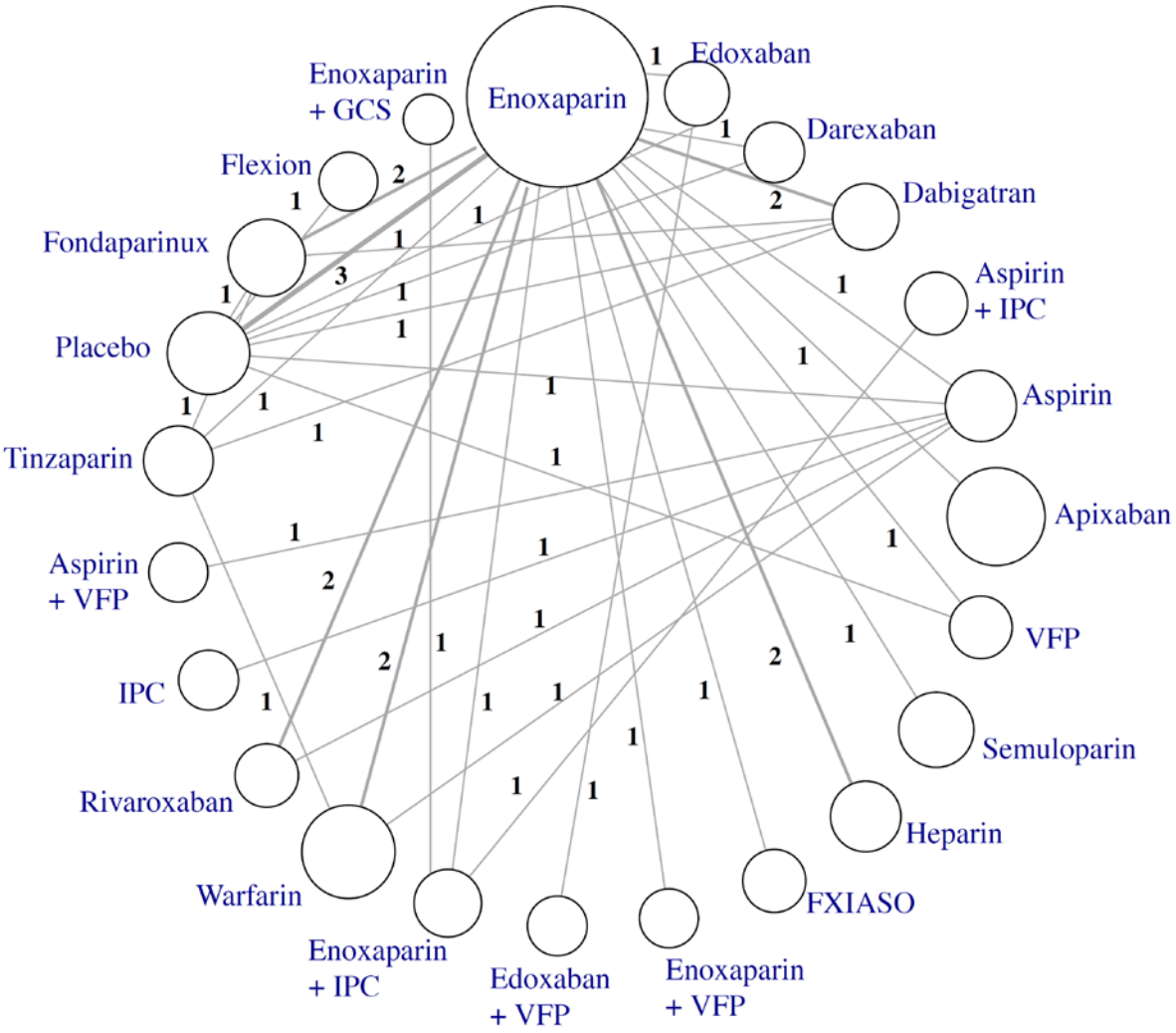


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 33 RCTs that evaluated at least two interventions and reported total DVT after TKR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included.[141] Hence, there were 32 RCTs in the network meta-analysis.[43, 52, 55, 65, 80, 87-90, 95-98, 101-106, 108, 114, 117, 120, 126, 139, 144, 147, 160-164] The RCTs compared pairs of interventions (29 RCTs), triplets of interventions (2 RCTs), or quadruplets of interventions (1 RCT). Across this study set, 23 interventions were evaluated (apixaban, aspirin, aspirin plus IPC, aspirin plus VFP, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, enoxaparin plus VFP, flexion, fondaparinux, FXIASO, UFH, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 253 possible pairwise comparisons, 34 are covered by direct study comparisons. Figure 48 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin plus GCS was directly compared with enoxaparin plus IPC only; IPC and aspirin plus VFP were directly compared with aspirin only; aspirin plus IPC was directly compared with enoxaparin plus IPC, edoxaban plus VFP was directly compared with edoxaban only.

Figure 48. Network of comparison of specific interventions for total deep vein thrombosis in total knee replacement



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after total knee replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: FXIASO = factor XI antisense oligonucleotide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, VFP = venous foot pump.

Appendix Table F7.6 shows the network meta-analysis pairwise results for all combinations of interventions. Results for the combination of enoxaparin plus GCS, the combination of enoxaparin plus VFP, and flexion devices were not estimable (due to the following: there was one RCT of enoxaparin plus GCS versus enoxaparin plus IPC which had small sample size and rare events [14/35 vs. 0/35]; there was one RCT of enoxaparin plus VFP versus enoxaparin which had zero events; there was one RCT of flexion device versus placebo which had zero events). The statistically significant differences between active interventions are highlighted here.

- **Rivaroxaban** had a lower odds of DVT compared with 8 active interventions.
- The combination of **aspirin plus VFP** had a lower odds of DVT compared with 6 active interventions
- **Apixaban** had a lower odds of DVT compared with 6 active interventions
- **Fondaparinux** had a lower odds of DVT compared with 6 active interventions
- **Edoxaban** had a lower odds of DVT compared with 6 active interventions
- **Dabigatran** had a lower odds of DVT compared with
    - *aspirin* (OR=0.348; 95% CrI 0.156 to 0.750)
    - *enoxaparin* (OR=0.569; 95% CrI 0.325 to 0.982)
    - *UFH* (OR=0.385; 95% CrI 0.189 to 0.777)
    - *tinzaparin* (OR=0.448; 95% CrI 0.189 to 0.998)
    - *warfarin* (OR=0.298; 95% CrI 0.152 to 0.569)
- **Darexaban** had a lower odds of DVT compared with
    - *aspirin* (OR=0.334; 95% CrI 0.12 to 0.913)
    - *UFH* (OR=0.371; 95% CrI 0.142 to 0.946)
    - *warfarin* (OR=0.288; 95% CrI 0.113 to 0.703)
- **IPC** had a lower odds of DVT compared with
    - *aspirin* (OR=0.386; 95% CrI 0.168 to 0.914)
    - *warfarin* (OR=0.333; 95% CrI 0.12 to 0.921)
- **FXIASO** had a lower odds of DVT compared with
    - *warfarin* (OR=0.410; 95% CrI 0.181 to 0.937)
- **Semuloparin** had a lower odds of DVT compared with
    - *warfarin* (OR=0.437; 95% CrI 0.234 to 0.789)
- **Enoxaparin** had a lower odds of DVT compared with
    - *warfarin* (OR=0.523; 95% CrI 0.361 to 0.742)

Summary

Overall, rivaroxaban had the highest probability (68%) of being among the top three interventions to prevent DVT after TKR, followed by flexion (65A%) and the combination of enoxaparin plus VFP (63%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%) and placebo (76%) (Table 19). The distribution of intervention ranks is provided in Figure 49.

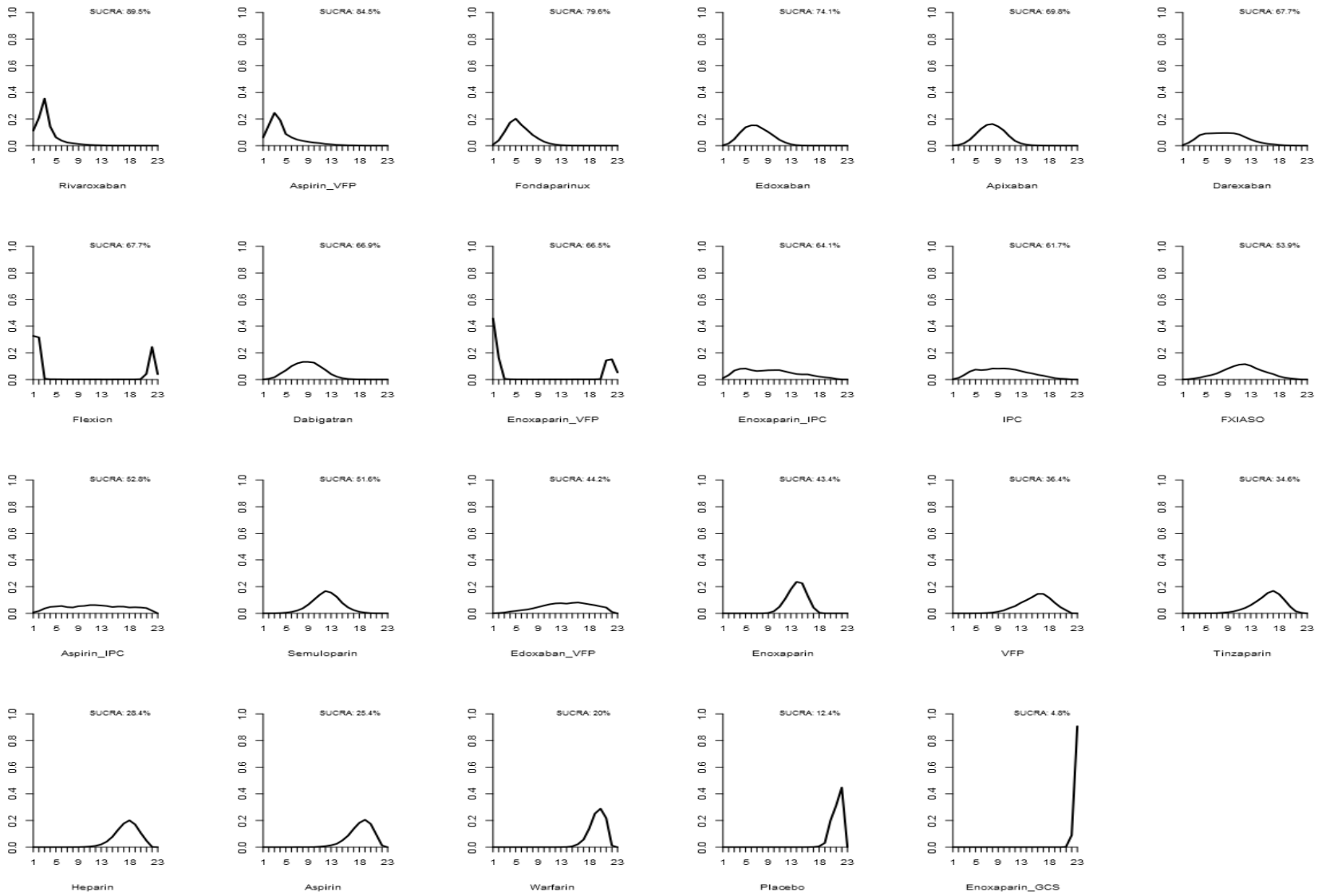
However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 19. Intervention ranking: Total knee replacement, intervention class comparisons to prevent deep vein thrombosis

	Top 3 Ranks	Bottom 3 Ranks
Rivaroxaban	68%	0%
Aspirin+VFP	46%	0%
Fondaparinux	15%	0%
Edoxaban	7%	0%
Apixaban	3%	0%
Darexaban	7%	0%
Flexion	65%	33%
Dabigatran	2%	0%
Enoxaparin+VFP	63%	35%
Enoxaparin+IPC	11%	1%
IPC	5%	1%
FXIASO	1%	0%
Aspirin+IPC	6%	6%
Semuloparin	0%	0%
Edoxaban+VFP	1%	5%
Enoxaparin	0%	0%
VFP	0%	2%
Tinzaparin	0%	2%
UFH	0%	5%
Aspirin	0%	11%
Warfarin	0%	23%
Placebo	0%	76%
Enoxaparin+GCS	0%	>99%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: FXIASO = factor XI antisense oligonucleotide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, UFH = unfractionated heparin, VFP = venous foot pump.

Figure 49. Network meta-analysis ranks of specific interventions to prevent total deep vein thrombosis in total knee replacement



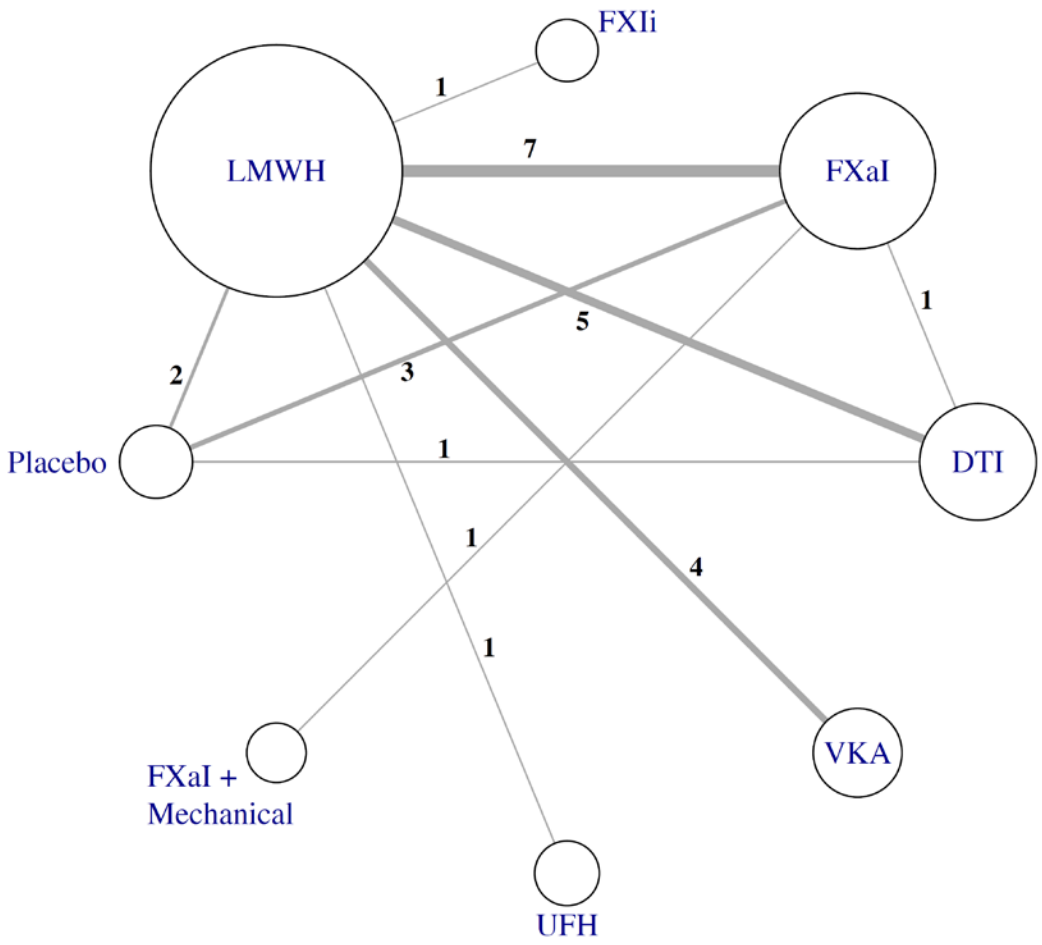
Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: FXIASO = factor XI antisense oligonucleotide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, SUCRA = surface under the cumulative ranking curve, VFP = venous foot pump.

Key Question 5 (TKR): Major Bleeding

Comparison of Classes

There were 23 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drug (aspirin) versus the combination of antiplatelet drug plus mechanical device did not connect to the network of evidence and was not included.[144] Hence, there were 22 RCTs in the network meta-analysis.[52, 55, 65, 80, 89, 91-93, 96-101, 104-108, 120, 126, 162] These RCTs compared pairs of intervention classes (19 RCTs) or triplets of intervention classes (2 RCTs). Across this study set, eight classes were evaluated (DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, UFH, VKA, placebo). Of the 28 possible pairwise comparisons, 10 are covered by direct study comparisons. Figure 50 illustrates the topology of the network. LMWH was the most common comparator, being directly compared with each of six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs). The combination of FXaI plus mechanical device was directly compared to FXaI only.

Figure 50. Network of comparison of intervention classes for major bleeding in total knee replacement



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after total knee replacement. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Appendix Table F7.7 shows the network meta-analysis pairwise results for all combinations of interventions classes. Results for comparisons versus FXIi were not estimable (due to the following: there was one RCT of FXIi versus enoxaparin which had zero events). There were no statistically significant differences between other classes (DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, UFH, VKA).

Summary

Across all comparisons, there were no statistically significant differences. Overall, VKA had the highest probability of being among the top three intervention classes (84%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did

not provide major bleeding data except for the one study of FXaI plus mechanical device versus FXaI. The interventions likely to be among the bottom three interventions were FXIi (68%) and FXaI (60%) (Table 20). The distribution of intervention ranks is provided in Figure 51.

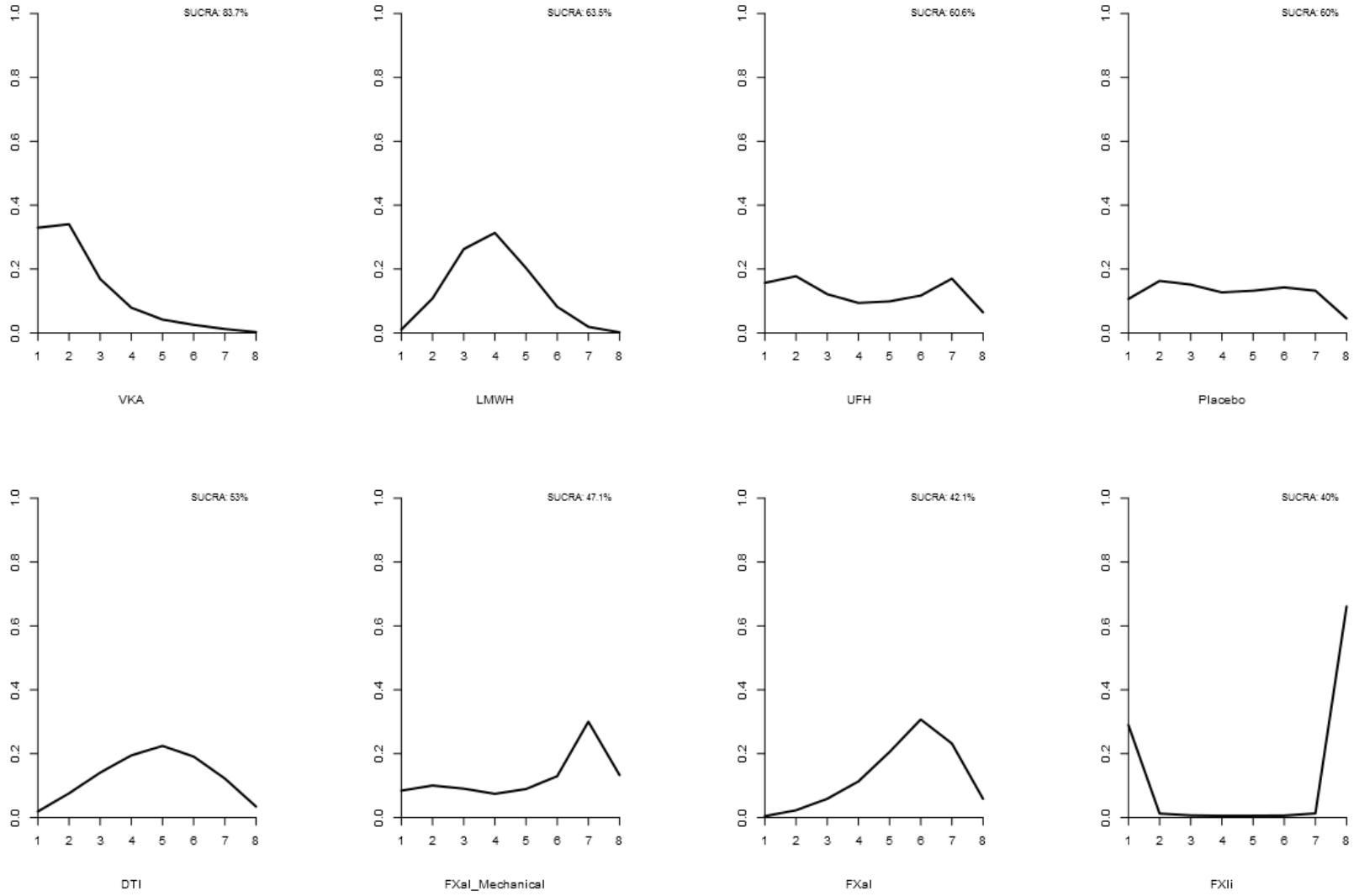
However, except for LMWH and FXaI (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. LMWH was more likely to result in fewer major bleeding events than FXaI.

Table 20. Class ranking: Total knee replacement, intervention class comparisons to avoid major bleeding

	Top 3 Ranks	Bottom 3 Ranks
VKA	84%	4%
LMWH	38%	10%
UFH	46%	35%
Placebo	42%	32%
DTI	23%	35%
FXaI+Mechanical Device	27%	56%
FXaI	9%	60%
FXIi	31%	68%

Percent likelihood that each class falls within the top 3 or bottom 3 classes in efficacy.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Figure 51. Network meta-analysis ranks of intervention classes to avoid major bleeding in total knee replacement

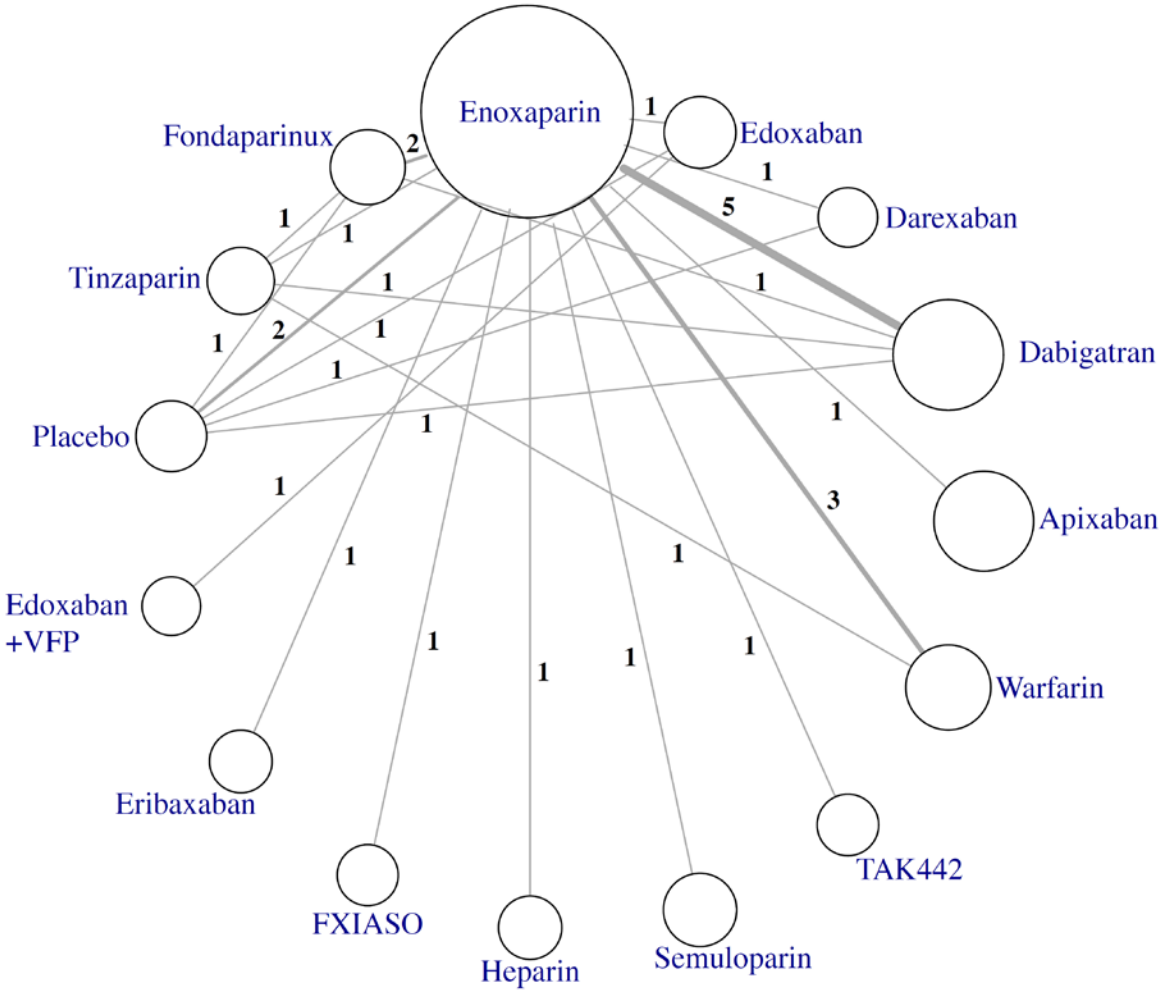


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were 24 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus the combination of aspirin plus VFP did not connect to the network of evidence and was not included.[144] Hence, there were 23 RCTs in the network meta-analysis.[52, 55, 65, 80, 89, 91-93, 96-101, 104-108, 114, 120, 126, 162] The RCTs compared pairs of interventions (21 RCTs), triplets of interventions (1 RCT), or quadruplets of interventions (1 RCT). Across this study set, 15 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, eribaxaban, fondaparinux, FXIASO, UFH, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 105 possible pairwise comparisons, 22 are covered by direct study comparisons. Figure 52 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with 13 other interventions; most frequently with dabigatran (5 RCTs). The combination of edoxaban plus VFP was directly compared with edoxaban only.

Figure 52. Network of comparison of specific interventions for major bleeding in total knee replacement



Topology map for network meta-analysis of different interventions of thromboprophylaxis to avoid major bleeding outcome after total knee replacement. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: FXIASO = factor XI antisense oligonucleotide.

Appendix Table F7.8 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with darexaban, edoxaban, edoxaban plus VFP, fondaparinux, and FXIASO were not estimable (due to the following: there was one RCT of darexaban versus enoxaparin versus placebo which had rare events [1/88 vs. 0/90 vs. 0/96]; there was one RCT of edoxaban versus placebo with zero events, another RCT of edoxaban versus enoxaparin with rare events [4/354 vs. 1/349], and a third RCT of edoxaban versus the combination of edoxaban plus VFP with rare events [3/62 versus 3/58]; two RCTs of fondaparinux had zero events and a third RCT versus enoxaparin had rare events [11/517 vs. 1/517]; there was one RCT of FXIASO versus enoxaparin that had zero events).

Among interventions with sufficient data to allow reliable estimates (apixaban, dabigatran,

enoxaparin, eribaxaban, UFH, semuloparin, TAK422, tinzaparin, and warfarin), no comparisons between interventions were found to have statistically significant differences in rates of major bleeding.

Summary

Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did not provide major bleeding data except for one study of the combination of edoxaban plus VFP versus edoxaban. The interventions likely to be among the bottom three interventions were darexaban (96%) and fondaparinux (65%) (Table 21). The distribution of intervention ranks is provided in Figure 53.

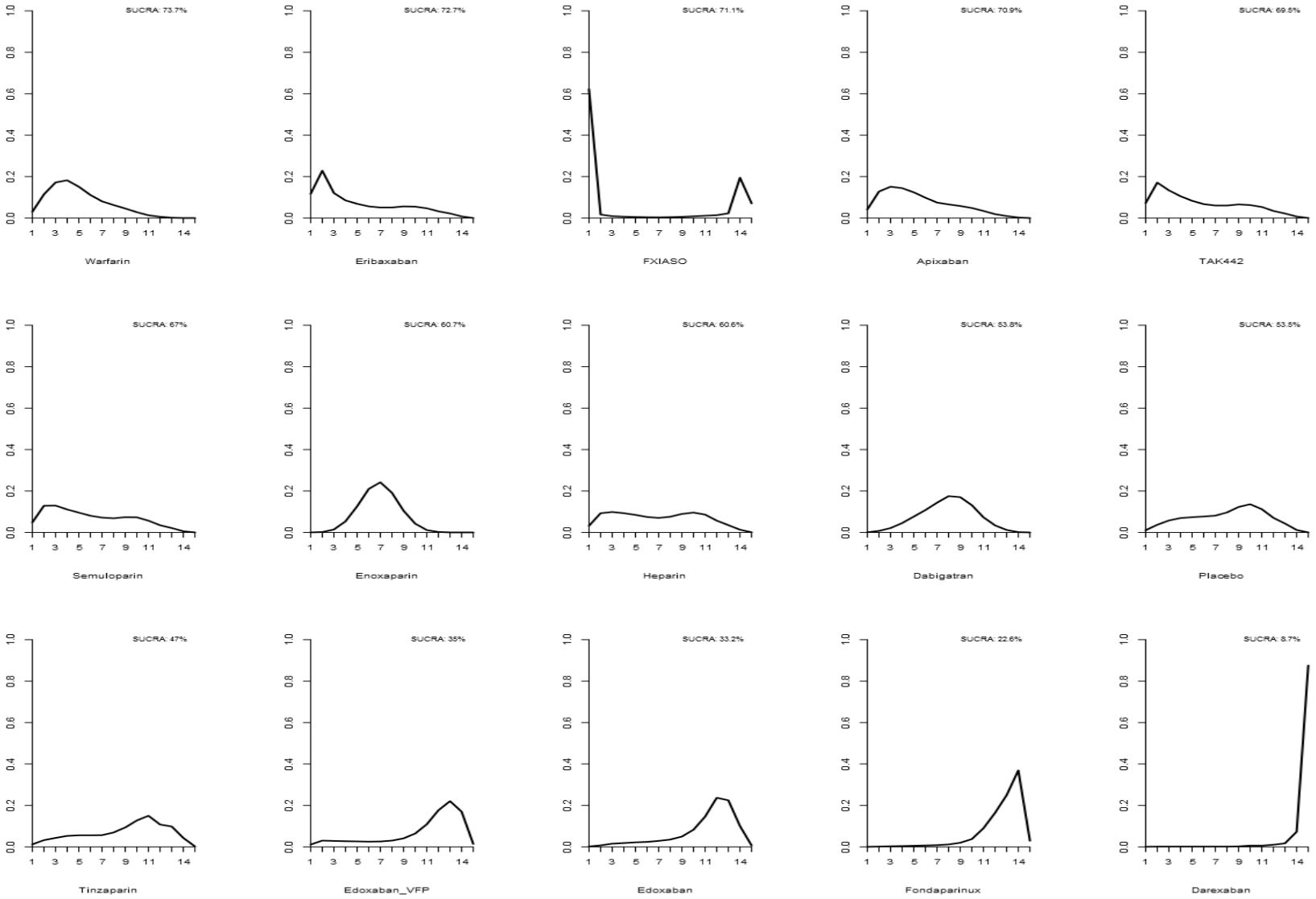
However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Table 21. Intervention ranking: Total knee replacement, intervention comparisons to avoid major bleeding

	Top 3 Ranks	Bottom 3 Ranks
Warfarin	31%	0%
FXIASO	67%	28%
Eribaxaban	46%	3%
Apixaban	32%	1%
TAK442	38%	3%
Semuloparin	31%	3%
Enoxaparin	2%	0%
UFH	22%	6%
Dabigatran	3%	1%
Placebo	10%	6%
Tinzaparin	9%	15%
Edoxaban+VFP	7%	41%
Edoxaban	2%	33%
Fondaparinux	0%	65%
Darexaban	1%	96%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviations: FXIASO = factor XI antisense oligonucleotide, UFH = unfractionated heparin.

Figure 53. Network meta-analysis ranks of specific interventions to avoid major bleeding in total knee replacement



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: IPC = intermittent pneumatic compression, SUCRA = surface under the cumulative ranking curve.

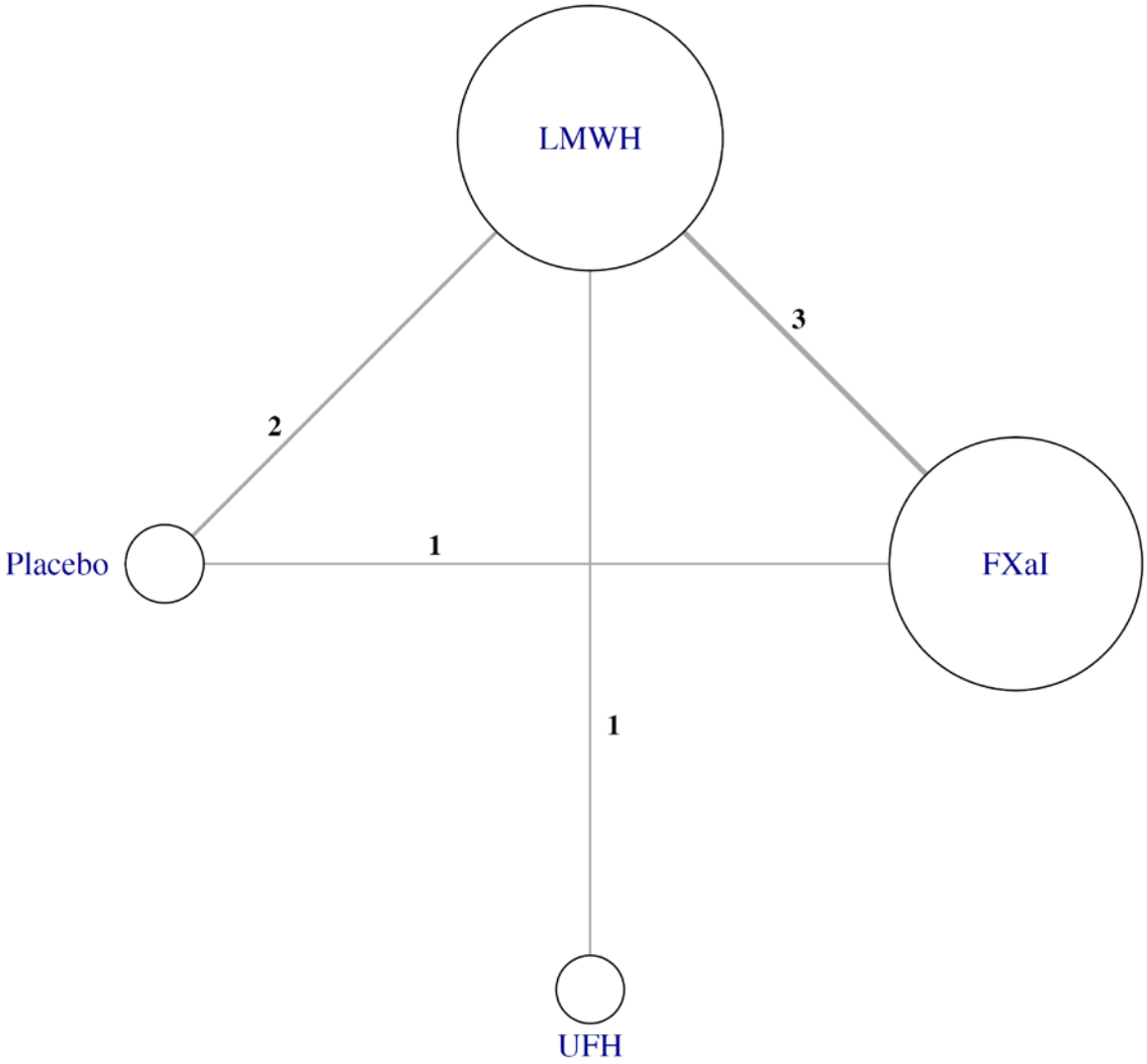
Key Question 5: Hip Fracture Surgery

Key Question 5 (HFx): Deep Vein Thrombosis, Total

Comparison of Classes

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drug (aspirin) versus a mechanical device did not connect to the network of evidence.[109] Hence there were five RCTs included in the network meta-analysis.[25, 111-113, 165] These RCTs compared pairs of intervention classes (four RCTs) or triplets of intervention classes (one RCT). Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. Figure 54 illustrates the topology of the network. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

Figure 54. Network of comparison of intervention classes for total deep vein thrombosis in hip fracture surgery



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for total deep vein thrombosis outcome after hip fracture surgery. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Appendix Table F7.9 shows the network meta-analysis pairwise results for all combinations of interventions classes. There were no statistically significant differences between classes.

Summary

There were no statistically significant differences. Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions (Table 22). The distribution of intervention ranks is provided in Figure

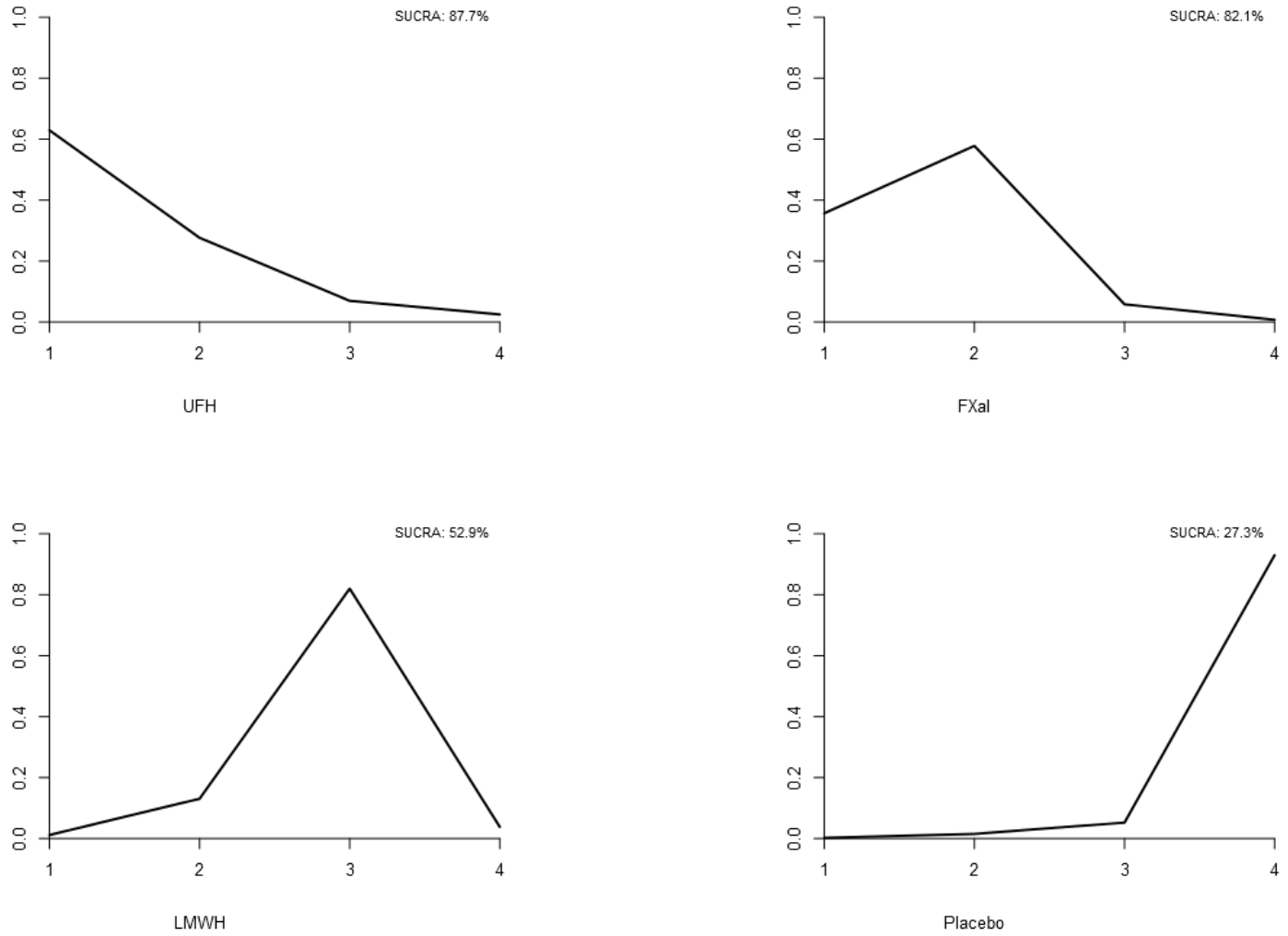
55. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

Table 22. Class ranking: Hip fracture surgery, intervention class comparisons to prevent deep vein thrombosis

	Top 2 Ranks	Bottom 2 Ranks
UFH	91%	9%
FXaI	93%	7%
LMWH	14%	86%
Placebo	2%	98%

Percent likelihood that each class falls within the top 2 or bottom 2 classes in efficacy.
Abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Figure 55. Network meta-analysis ranks of intervention classes to prevent total deep vein thrombosis in hip fracture surgery

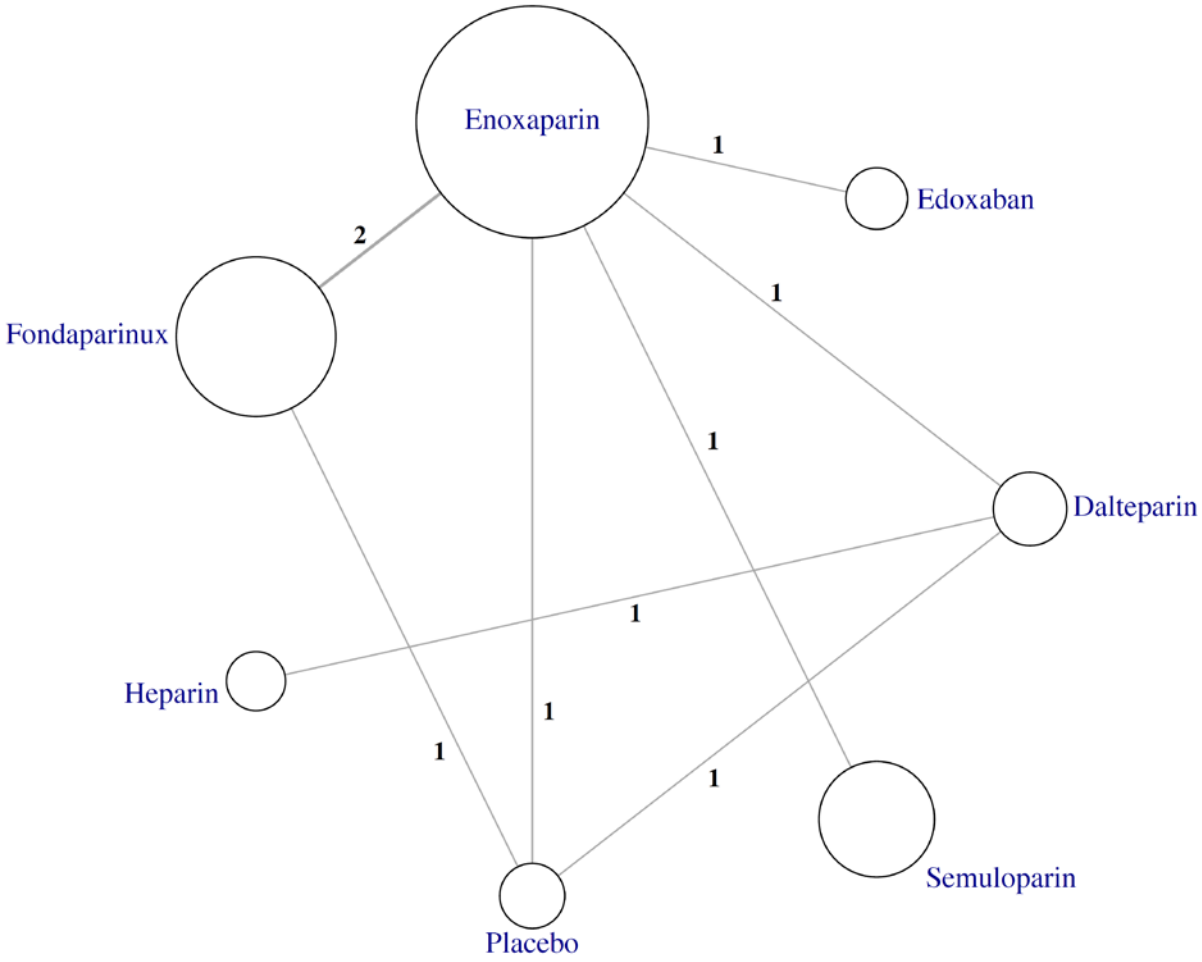


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, UFH = unfractionated heparin.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. As with the analysis by class, there was one RCT of aspirin versus VFP which did not connect to the network of evidence.[109] Hence there were seven RCTs included in the network meta-analysis.[25, 111-114, 118, 165] These RCTs compared pairs of interventions (six RCTs) or triplets of interventions (one RCT). Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, UFH, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. Figure 56 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with five other interventions. UFH was directly compared with dalteparin only.

Figure 56. Network of comparison of specific interventions for total deep vein thrombosis in hip fracture surgery



Topology map for network meta-analysis of different interventions of thromboprophylaxis for total deep vein thrombosis outcome after hip fracture surgery. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.

Appendix Table F7.10 shows the network meta-analysis pairwise results for all combinations of interventions. The statistically significant differences between active interventions are highlighted here.

- **Fondaparinux** had a lower odds of DVT compared with
    - *enoxaparin* (OR=0.340; 95% CrI 0.105 to 0.970).

Summary

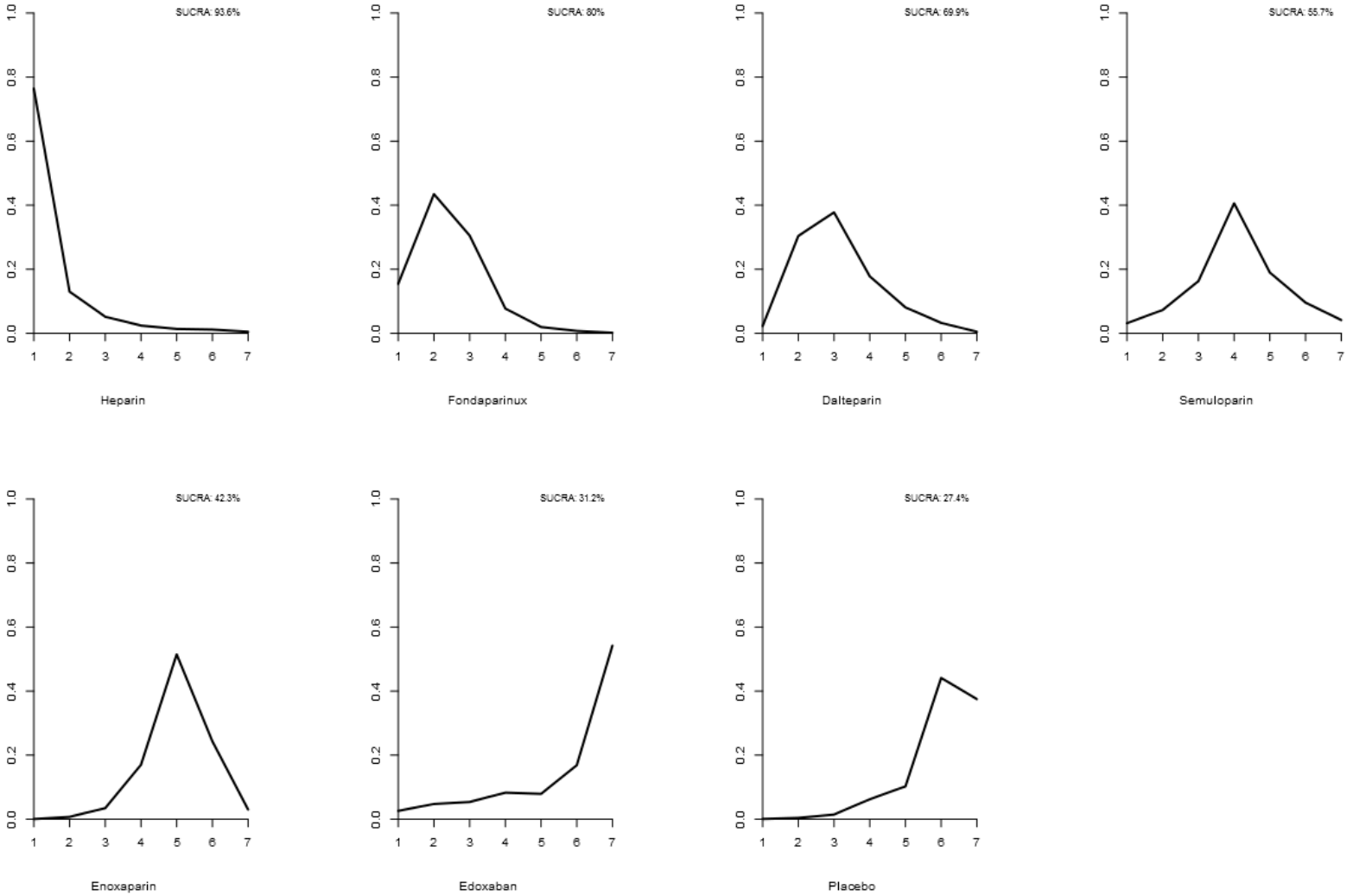
Overall, UFH (95%) had the highest probability of being among the top three interventions to prevent DVT after HFx surgery, followed by fondaparinux (89%) and dalteparin (70%). The other three interventions were likely to be among the bottom three interventions: placebo (92%), enoxaparin (79%), and edoxaban (79%) (Table 23). The distribution of intervention ranks is provided in Figure 57. However, no intervention was directly compared to two other interventions by at least two RCTs.

Table 23. Intervention ranking: Hip fracture surgery, intervention comparisons to prevent deep vein thrombosis

	Top 3 Ranks	Bottom 3 Ranks
UFH	95%	3%
Fondaparinux	89%	3%
Dalteparin	70%	12%
Semuloparin	27%	33%
Enoxaparin	4%	79%
Edoxaban	13%	79%
Placebo	2%	92%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.
Abbreviation: UFH = unfractionated heparin.

Figure 57. Network meta-analysis ranks of specific interventions to prevent total deep vein thrombosis in hip fracture surgery



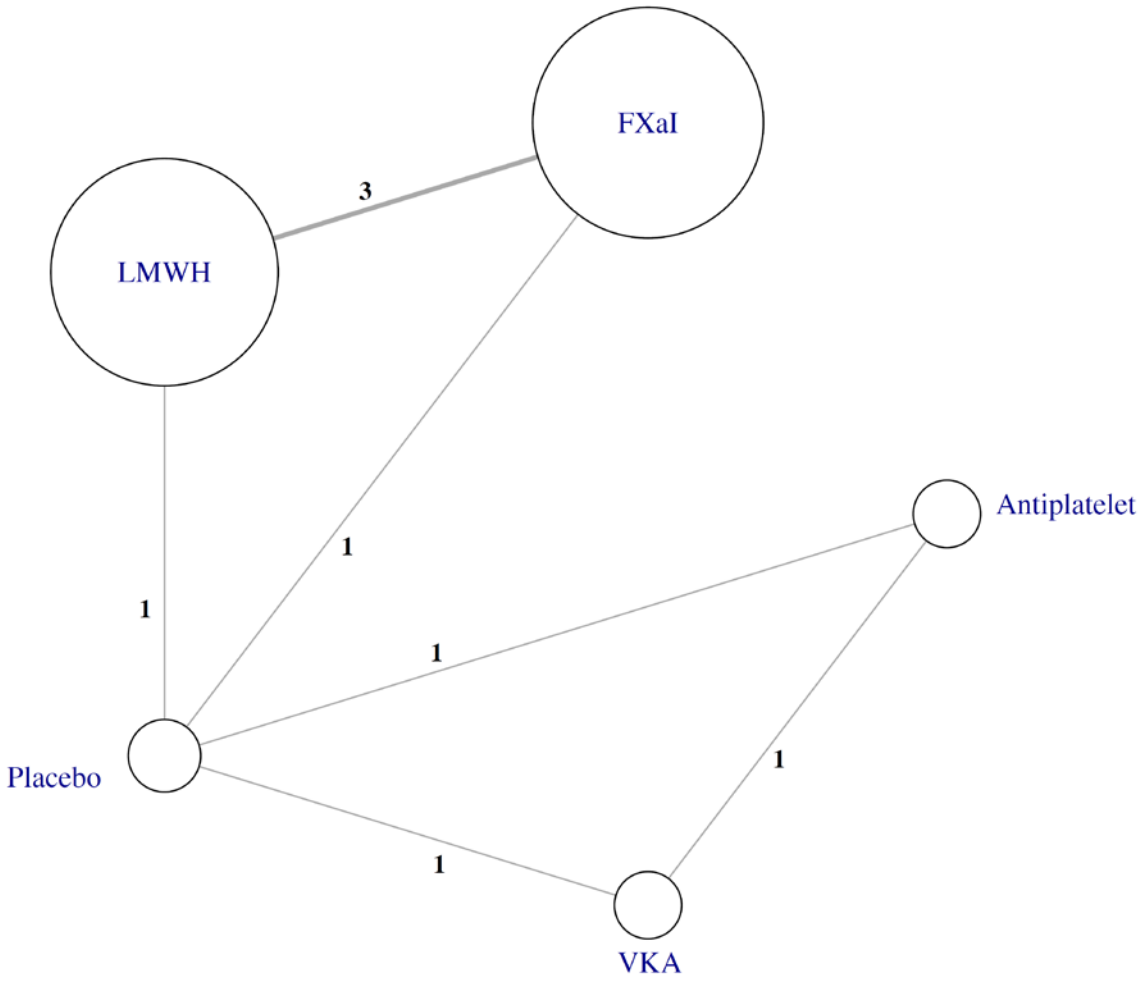
Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others. Abbreviations: SUCRA = surface under the cumulative ranking curve.

Key Question 5 (HFx): Major Bleeding

Comparison of Classes

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery.[25, 110-112] The RCTs compared pairs of intervention classes (2 RCTs) or triplets of intervention classes (two RCTs). Across this study set, five classes were evaluated (antiplatelet drug [aspirin], FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. Figure 58 illustrates the topology of the network. Placebo was the most common comparator, being directly compared with each of the five other intervention classes.

Figure 58. Network of comparison of intervention classes for major bleeding in hip fracture surgery



Topology map for network meta-analysis of different classes of thromboprophylaxis interventions for major bleeding outcome after hip fracture surgery. Nodes represent different classes of interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.

Abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Appendix Table F7.11 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons versus antiplatelet drug and VKA were not estimable (due to the following: there was one RCT of antiplatelet drug versus VKA versus placebo which had a small sample size and rare events [1/66 vs. 5/65 vs. 5/63]). Among interventions with sufficient data to allow reliable estimates (FXaI and LMWH), the comparison between interventions was not statistically significant regarding risk of major bleeding.

Summary

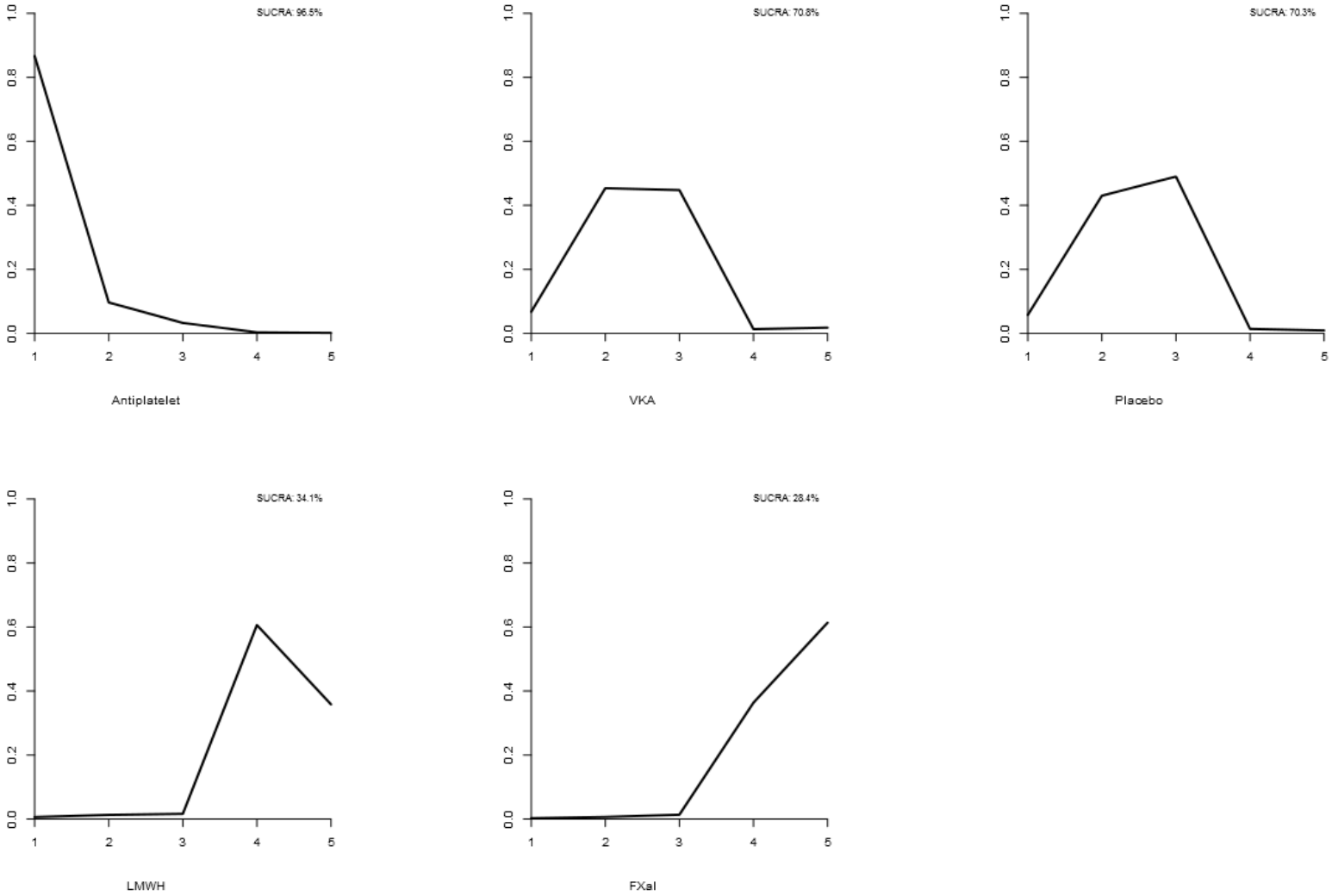
There were no statistically significant differences. Overall, antiplatelet drug (aspirin) had the highest probability of being among the top two interventions (96%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (52%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (96%) (Table 24). The distribution of intervention ranks is provided in Figure 59. However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Table 24. Class ranking: Hip fracture surgery, intervention comparisons to avoid major bleeding

	Top 2 Ranks	Bottom 2 Ranks
Antiplatelet	96%	0%
VKA	52%	3%
Placebo	49%	2%
LMWH	2%	96%
FXaI	1%	98%

Percent likelihood that each class falls within the top 2 or bottom 2 classes in efficacy.
Abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Figure 59. Network meta-analysis ranks of intervention classes to avoid major bleeding in hip fracture surgery

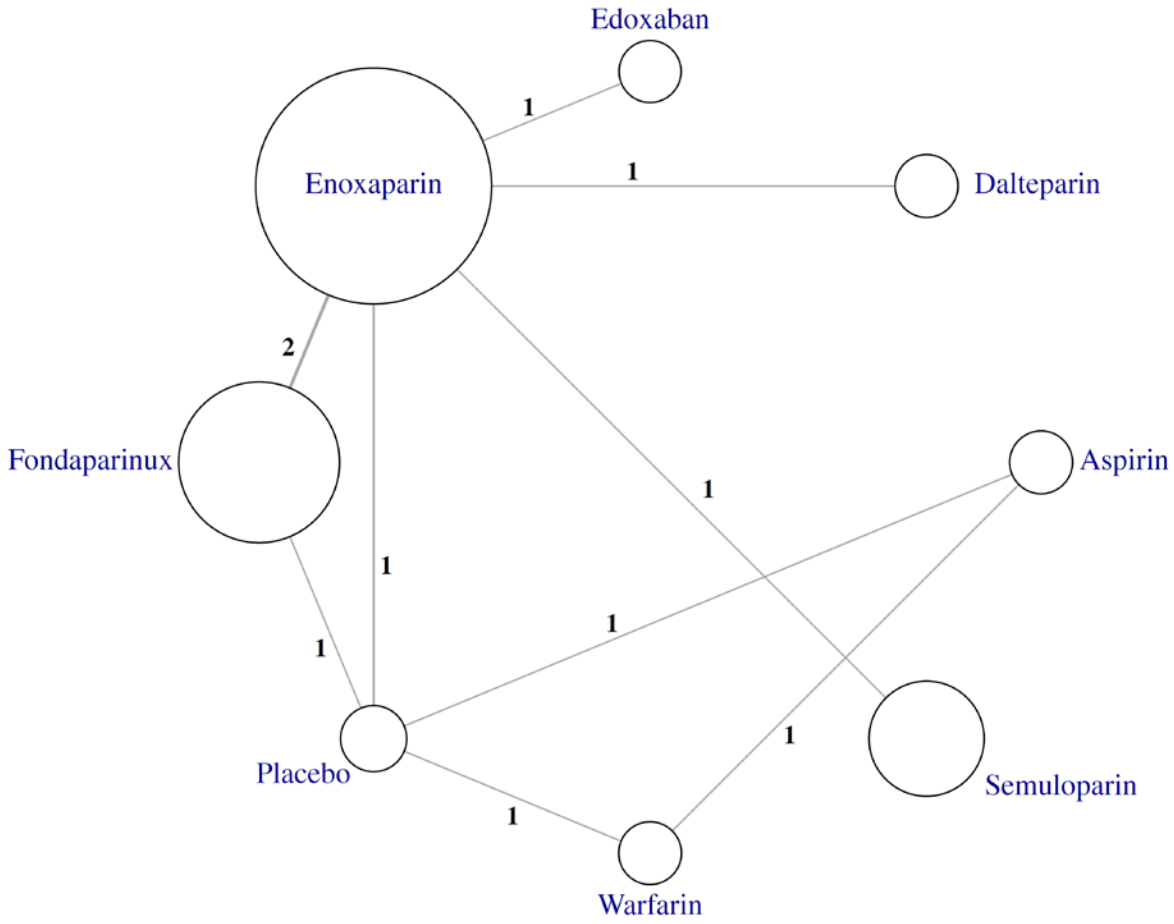


Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention class based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, SUCRA = surface under the cumulative ranking curve, VKA = vitamin K antagonist.

Comparison of Specific Interventions

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery.[25, 110-112, 114, 118] The RCTs compared pairs of interventions (four RCTs) or triplets of interventions (two RCTs). Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. Figure 60 illustrates the topology of the network. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

Figure 60. Network of comparison of specific interventions for major bleeding in hip fracture surgery



Topology map for network meta-analysis of different interventions of thromboprophylaxis for major bleeding outcome after hip fracture surgery. Nodes represent different interventions included in the analysis. Lines between nodes indicate the pairs of intervention classes that were compared directly within trials. The thickness of the lines is proportional to the number of trials directly comparing pairs of interventions, as indicated by the associated number.

Appendix Table F7.12 shows the network meta-analysis pairwise results for all combinations of interventions. Results for comparisons with aspirin and warfarin were not estimable (due to the following: there was one RCT of aspirin versus warfarin versus placebo which had a small sample size and rare events [1/66 vs. 5/65 vs. 5/63]). Among interventions with sufficient data to allow reliable estimates (dalteparin, edoxaban, fondaparinux, and semuloparin), all comparisons between interventions were not statistically significant regarding risk of major bleeding.

Summary

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (95%) and warfarin (94%). The interventions likely to be among the bottom three interventions were fondaparinux (82%), semuloparin (77%), and enoxaparin (67%) (Table 25). The distribution of intervention ranks is provided in Figure 61.

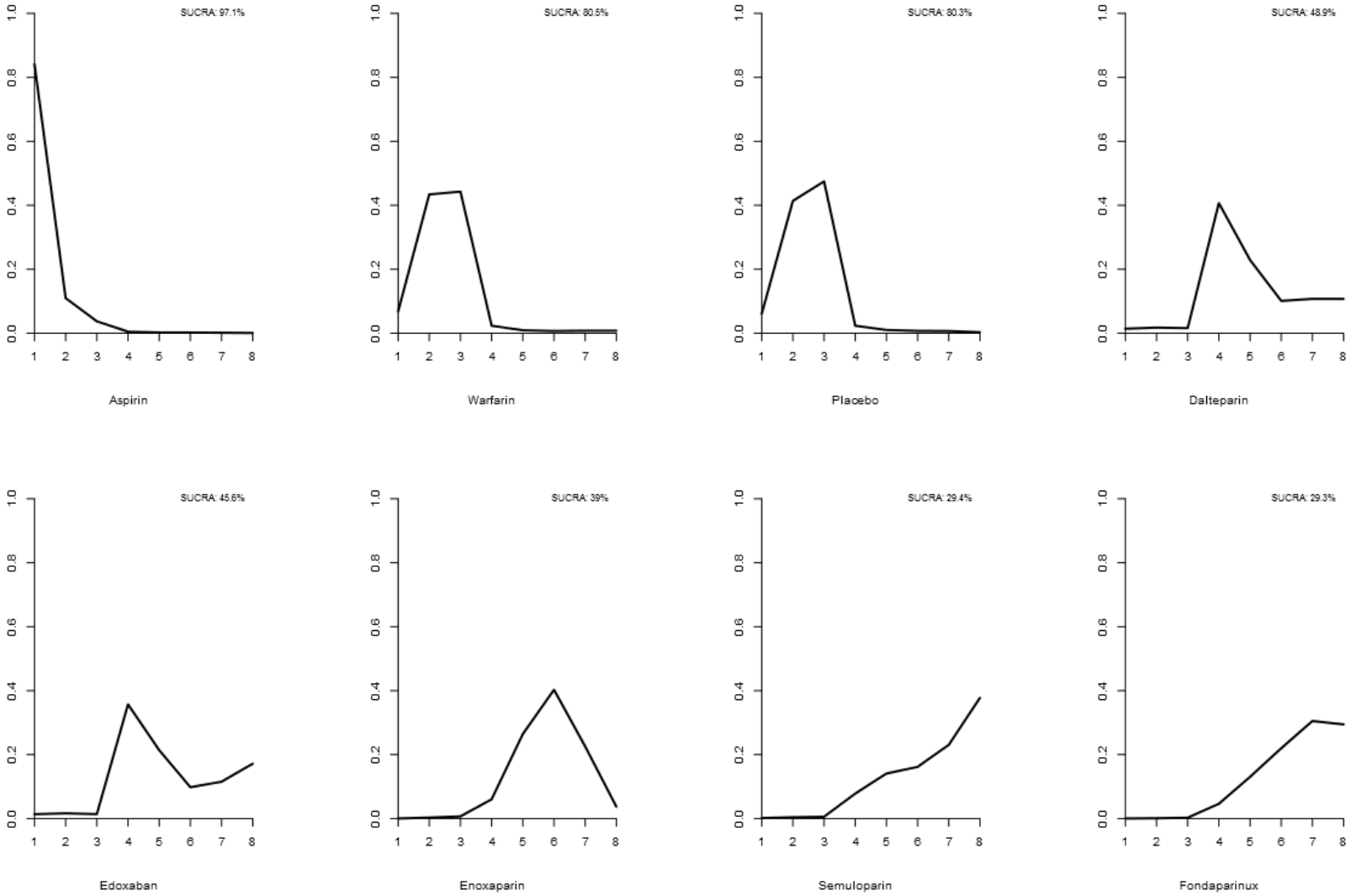
However, only enoxaparin and fondaparinux were directly compared by two RCTs, with similar risk of major bleeding.

Table 25. Intervention ranking: Hip fracture surgery, intervention comparisons to avoid major bleeding

	Top 3 Ranks	Bottom 3 Ranks
Aspirin	99%	0%
Warfarin	94%	2%
Placebo	95%	2%
Dalteparin	5%	32%
Edoxaban	4%	38%
Enoxaparin	1%	67%
Semuloparin	1%	77%
Fondaparinux	0%	82%

Percent likelihood that each intervention falls within the top 3 or bottom 3 interventions in efficacy.

Figure 61. Network meta-analysis ranks of specific interventions to avoid major bleeding in hip fracture surgery



Distribution of probability (y-axis) of treatment rankings (x-axis) by intervention based on network meta-analysis. Lower ranks indicate lower odds of outcome (greater benefit) with the given intervention compared with others.
Abbreviations: SUCRA = surface under the cumulative ranking curve.

Key Question 5 (All Surgeries): Total DVT and Major Bleeding Absolute Rate Estimates, by Surgery and Class

Based on RCTs included in the network meta-analysis, we estimated rates of total DVT and major bleeding for each intervention class (with estimable data), by surgery type. These estimates are based on the summary estimates (median, minimum, and maximum) of total DVT and major bleeding for patients who received LMWH (the class with the most RCT data) and the OR for each available class compared to LMWH. The estimates are presented in Table 26.

Table 26. Estimated proportion of patients with total deep vein thrombosis after surgery, by intervention class

Surgery	Class	Total DVT Event Proportion, Median (Range)	Major Bleeding Event Proportion, Median (Range)
THR	LMWH + Mechanical Device	0.026 (<0.001, 0.193)	No data
	FXaI	0.076 (0.001, 0.423)	0.023 (0.002, 0.075)
	FEI	0.084 (0.001, 0.449)	Not estimable
	DTI	0.085 (0.001, 0.451)	0.022 (0.002, 0.072)
	Mechanical Devices	0.100 (0.001, 0.497)	Not estimable
	Antiplatelet	0.100 (0.001, 0.495)	Not estimable
	LMWH	0.121 (0.002, 0.548)	0.017 (0.001, 0.057)
	VKA	0.170 (0.002, 0.644)	0.009 (0.001, 0.030)
	UFH	0.176 (0.002, 0.653)	0.037 (0.003, 0.116)
TKR	LMWH + Mechanical Device	0.099 (0.001, 0.328)	
	FXaI	0.111 (0.001, 0.356)	0.026 (0.004, 0.089)
	Antiplatelet + Mechanical Device	0.113 (0.001, 0.360)	No data
	LMWH + Mechanical Device	0.126 (0.002, 0.390)	No data
	DTI	0.131 (0.002, 0.400)	0.019 (0.003, 0.066)
	FXIi	0.172 (0.002, 0.480)	Not estimable
	FXaI + Mechanical Device	0.207 (0.003, 0.537)	0.028 (0.004, 0.096)
	LMWH	0.209 (0.003, 0.539)	0.015 (0.002, 0.052)
	Mechanical Devices	0.218 (0.003, 0.553)	No data
	UFH	0.281 (0.004, 0.634)	0.015 (0.002, 0.053)
	VKA	0.323 (0.005, 0.679)	0.007 (0.001, 0.026)
	Antiplatelet	0.351 (0.006, 0.706)	No data
HFx	UFH	0.095 (0.002, 0.291)	No data
	FXaI	0.124 (0.002, 0.357)	0.028 (0.004, 0.043)
	LMWH	0.254 (0.005, 0.571)	0.023 (0.004, 0.035)
	Antiplatelet	No data	Not estimable
	VKA	No data	Not estimable

Within surgery type, intervention classes ordered from lowest to highest estimated DVT rates.
Abbreviations: CI = confidence interval, DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, HFx = hip fracture surgery, LMWH = low molecular weight heparin, THR = total hip replacement, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Key Question 6: Comparison of Different Start Times of Thromboprophylaxis Interventions

Key Question 6: Total Hip Replacement

Key Question 6 (THR): LMWH Preoperative Versus Postoperative Start

Two RCTs (N=1063) compared LMWH started preoperatively versus postoperatively (Table 27).[81, 166] One study found no significant difference in total DVT and proximal DVT, and reported no total PE, and no fatal PE. The other study found no significant difference in symptomatic PE. The two studies reported symptomatic DVT; one found no significant difference, and the other reported no events.

One RCT found no significant difference in major bleeding and 30-day mortality, and reported no fatal bleeding. The other study found no significant difference in bleeding leading to reoperation. Two studies found no significant difference in bleeding at surgical site or joint.

The studies did not report on adherence.

Key Question 6: Total Knee Replacement

No eligible studies evaluated patients with TKR.

Key Question 6: Hip Fracture Surgery

No eligible studies evaluated patients with HFx surgery.

Table 27. Results summary: Total hip replacement, treatment initiation time comparisons

Comparison	Outcome	Studies, N	Patients, N	OR (95% CI), 1* *or Summary OR (95% CI) †*	OR (95% CI), 2*	OR (95% CI), 3*	No Events‡
LMWH, preop vs. postop	PE, Total	1	983	No estimate			1 RCT
	PE, Fatal	1	983	No estimate			1 RCT
	PE, Symptomatic	1	80	0.33 (0.01, 8.22)			
	DVT, Total	1	673	0.79 (0.50, 1.27)			
	DVT, Symptomatic	2	753	0.49 (0.17, 1.45)			1 RCT
	DVT, Proximal	1	712	1.01 (0.20, 5.05)			
	Bleeding, Major	1	983	1.17 (0.69, 1.97)			
	Bleeding, Fatal	1	983	No estimate			1 RCT
	Bleeding, Leading to reoperation	1	80	3.08 (0.12, 77.8)			
	Bleeding, Surgical site/joint	2	1063	0.73 (0.15, 3.49)	1.17 (0.69, 1.99)		
	Mortality, 30 day or in-hospital	1	983	4.93 (0.24, 103)			

All outcomes for all pairwise comparisons with data from at least one study. If 3 or fewer randomized controlled trials (RCT) with analyzable data (i.e., at least 1 event per study) then each study's odds ratio (OR) is listed in ascending order from left to right. If there were ≥4 analyzable studies, then meta-analysis was conducted and summary OR is reported. These are indicated by italics and by MA (meta-analysis) in the study number column. Statistically significant OR estimates are in bold text. The corresponding studies for each analysis can be found in Appendix F.
Other abbreviations: DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venothromboembolism, LMWH = low molecular weight heparin, Preop = preoperative, Postop = postoperative.

* If meta-analysis was not conducted (if there were <4 meta-analyzable trials), the individual studies' results are presented across OR 1, 2, and 3, from lowest to highest. Statistically significant estimates are in bold. OR <1 favor the first intervention (e.g., for PE, Symptomatic, OR = 0.33 favors preoperative start).
† Summary odds ratios (from meta-analysis) are italicized. Statistically significant estimates are in bold.
‡ Number of RCTs with no events in both arms.

Overall Summary and Strength of Evidence

Total Hip Replacement

Across Key Questions, 85 eligible studies evaluated thromboprophylaxis interventions in patients who underwent THR. The largest number compared different classes of interventions (relevant to Key Questions 1 and 5). The most commonly evaluated intervention class was LMWH, mostly in comparison with DTI, FXaI, UFH, and VKA. Other interventions were relatively infrequently evaluated in comparative effectiveness trials (i.e., comparisons of active, nonplacebo interventions). The most commonly evaluated outcomes were total DVT and major bleeding. Strength of evidence (SoE) is summarized in Table 28.

Key Question 1: Comparison of Intervention Classes in THR Studies

Note that network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- There were 46 RCTs and 5 NRCSs that compared classes of interventions in patients undergoing THR.
- Pairwise comparisons between classes had sufficient data (i.e., not "insufficient") for only six pairs of classes.
    - **LMWH vs. DTI**: Across outcomes there is a tradeoff between the two drug classes. Moderate SoE favors DTI to prevent total DVT and, separately, proximal DVT, but low SoE favors LMWH to avoid major bleeding.
    - **LMWH vs. FXaI**: Across outcomes, the evidence is inconsistent. The studies found that FXaI better lowers the risk of total VTE (low SoE), total DVT (moderate SoE), and proximal DVT (moderate SoE), but LMWH better lowers the risk of symptomatic VTE (low SoE) and symptomatic DVT (low SoE). There was high SoE that LMWH is better to prevent major bleeding, but both classes were similar in rates of study-defined serious adverse events (moderate SoE). The inconsistencies in these finding suggest important reporting bias.
    - **LMWH vs. UFH**: Overall, favors LMWH, with lower risk of total PE (high SoE), proximal DVT (moderate SoE), and major bleeding (moderate SoE); risk of total DVT was similar between drug classes (moderate SoE).
    - **LMWH vs. VKA**: Overall unclear. There is insufficient evidence regarding the relative benefit of either drug class to lower the risk of any VTE outcome, but VKA results in lower risk of major bleeding (high SoE).
    - **LMWH vs. aspirin**: Based primarily on a very large propensity-score-adjusted NRCS, LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding (all low SoE).
    - **Mechanical devices vs. VKA**: Overall, unclear. VKA results in lower risk of proximal DVT (high SoE), but insufficient evidence all favors mechanical devices to lower the risk of total DVT, and adverse events data have not been reported.
    - For all other class comparisons and outcomes there was insufficient evidence.

    - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.
- A within-study subgroup analysis by chronic kidney disease category was inconclusive regarding differential risks of bleeding with LMWH and DTI.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for at least one outcome for six pairs of classes (Table 28). For the comparison of LMWH versus DTI, among four RCTs, three favored DTI to prevent total DVT and to prevent proximal DVT. Meta-analysis of the four trials found a nonsignificant difference between drug classes regarding major bleeding favoring LMWH.

For the comparison of LMWH versus FXaI, among 13 RCTs, there is high risk of reporting bias. Most meta-analyses of VTE outcomes significantly favored FXaI (total VTE [6 RCTs, low SoE], total DVT [10 RCTs, moderate SoE], and proximal DVT [10 RCTs, moderate SoE]). The meta-analyses of symptomatic VTE (7 RCTs, low SoE) and symptomatic DVT (9 RCTs, low SoE) found no significant differences between LMWH and FXaI, but favored LMWH; however, these RCTs mostly did not report other VTE outcomes. Major bleeding was significantly less likely with LMWH (10 RCTs, high SoE), but there was no significant difference in study-defined serious adverse events (5 RCTs, moderate SoE). Given the inconsistent findings across VTE outcomes, the relative benefit of either drug class is unclear.

Among 3 RCTs of LMWH versus mechanical devices, none found significant differences for heterogeneous VTE outcomes. A NRCS found no difference in total PE. A single RCT reported significantly more frequent major bleeding with LMWH. Overall, the evidence was deemed to be insufficient to make conclusions about relative effect or harms between the two intervention classes.

From 10 RCTs, meta-analyses of LMWH versus UFH significantly favored LMWH to prevent total PE (8 RCTs, high SoE) and proximal DVT (6 RCTs, moderate SoE) and to avoid major bleeding (6 RCTs, moderate SoE), but showed no statistically significant difference in total DVT (10 RCTs, moderate SoE). Overall, the evidence favors LMWH.

Meta-analysis of the 4 RCTs of LMWH versus VKA found significantly lower rates of major bleeding with VKA (high SoE); however, the evidence regarding VTE is insufficient.

One very large NRCS (N=108,584) and another smaller NRCS (N=1,533) compared LMWH versus antiplatelet drug (aspirin). The evidence suggests both drug classes have similar effects and harms. In both adjusted and propensity-score matched analyses, the very large NRCS found no differences in rates of total PE, symptomatic DVT, and major bleeding (all low SoE).

Three RCTs evaluated mechanical devices versus VKA, overall yielding unclear findings regarding relative benefits and harms. The studies favored VKA to prevent proximal DVTs (high SoE), but insufficient evidence for total DVT favored mechanical devices, and there was no evidence regarding adverse events.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drug versus VKA (2 RCTs, one NRCS), LMWH versus antiplatelet drug (2 NRCSs),

antiplatelet drug versus mechanical device (1 NRCS), mechanical devices versus UFH (1 RCT), DTI versus FXaI (1 RCT), DTI versus UFH (2 RCTs), and FEI versus FXaI (1 RCT).

Subgroup Analysis

One RCT reported results for serious bleeding by level of chronic kidney disease in a comparison of LMWH and DTI. Event rates were low for all participants (2% in both the desirudin and the enoxaparin arms). They reported that for chronic kidney disease category 3B (n=569), more patients experienced a major bleed in the desirudin arm than in the enoxaparin arm, although the difference was not statistically significant (1.8% vs. 0.3%; P = 0.112). For chronic kidney disease category 3A (n=758), the rates were the same (0.3% in both arms). For chronic kidney disease categories 1-2 (n=700), DVT rates were lower in the enoxaparin arm (0.6% vs. 0%).

Studies were generally homogeneous in terms of patient eligibility criteria, such that most studies included all-comers without eligibility restrictions based on demographics, or other major patient or surgery subtypes. While some studies were restricted based on past bleeding history or chronic antiplatelet or VKA use, no RCTs were restricted to the converse populations (only patients with bleeding history or on antithrombotic medication). Thus, across-study comparisons of subgroup factors are limited.

Among THR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus UFH. For total DVT, by random effects model metaregression no significant difference (P=0.51) was found between the eight industry-funded studies (summary OR 0.91, 95% CI 0.59 to 1.41) and the two studies without reported industry support (summary OR 0.71, 95% CI 0.38 to 1.32). Similarly, for major bleeding, no significant difference (P=0.95) was found between the four industry-funded studies (summary OR 0.62, 95% CI 0.13 to 2.93) and the two studies without industry support (summary OR 0.56, 95% CI 0.26 to 1.20).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.56) was found between the five Asian studies (summary OR 1.63, 95% CI 0.81 to 3.31) and the four non-Asian studies (summary OR 2.08, 95% CI 1.40 to 3.09) by random effects model metaregression. The non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. Overall, the same percentage of Asian and non-Asian study participants had a DVT among these RCTs (4.7%). Similarly, for major bleeding, no significant difference (P=0.16) was found between the four Asian RCTs with major bleeding events (summary OR 1.95, 95% CI 0.46 to 8.22) and the five non-Asian studies (OR 0.68, 95% CI 0.49 to 0.94). Again, the non-Asian studies included more patients, largely explaining the difference in statistical significance between the two sets of studies. The Asian RCTs had relatively few events, with an overall major bleeding rate of 0.7 percent compared to 1.5 percent among all non-Asian RCTs (P=0.041); however, if the European study with an atypically high reported major bleeding rate (3.5%) is excluded, the non-Asian RCTs have a major bleeding rate of 0.9 percent, similar to the reported Asian rate (P=0.59).

Key Question 2: Comparison of Within-Class Interventions in THR Studies

Note that network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of thromboprophylaxis compared specific interventions within any given class (3 for THR) (Table 28). No comparison was evaluated by more than two studies.

In patients undergoing THR, one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations in THR Studies

Key Points

- There were 22 RCTs and 2 NRCSs that compared different intervention doses or durations in patients undergoing THR
- **FXaI low vs. high dose**: Evidence for high versus low dose FXaI is unclear. There is low SoE that higher dose FXaI (darexaban 30 to 60 mg, edoxaban 30 mg) has a lower risk of total VTE than lower dose FXaI (darexaban 10 to 15 mg, edoxaban 15 mg), but there is insufficient evidence for other outcomes, including adverse events.
- **LMWH low vs. high dose**: There is evidence of a tradeoff between low and high dose LMWH. Higher dose LMWH (e.g., enoxaparin 40 mg) results in a lower risk of total DVT than lower dose LMWH (e.g., enoxaparin 20 to 30 mg) (low SoE), but both high and low dose LMWH result in similar risk of proximal DVT. Lower dose LMWH has a lower risk of major bleeding than higher dose LMWH (moderate SoE).
- **LMWH short vs. long duration**: The evidence supports longer duration LMWH. Longer duration LMWH (>2 weeks) results in lower risk of total PE (low SoE), total DVT (high SoE), and proximal DVT (moderate SoE) than shorter duration LMWH (up to 10 days or to hospital discharge); bleeding events were rare in the LMWH studies yielding insufficient evidence regarding relative difference in risk.

Summary Results

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level analyses; specific intervention comparisons were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

For three pairwise comparisons of dose or treatment duration, there was sufficient data (Table 28). Among four RCTs comparing FXaI low versus high doses, meta-analysis yielded a nonsignificant effect favoring high dose FXaI to prevent total VTE. Data were insufficient for other outcomes.

Five RCTs compared LMWH low versus high doses. Meta-analysis of the 5 RCTs found a nonsignificant effect on total DVT favoring higher dose LMWH. Meta-analysis found no difference in effect on proximal DVTs (4 RCTs). By meta-analysis, there was significantly less risk of major bleeding with lower dose LMWH (4 RCTs).

Among 6 RCTs of LMWH short versus long duration treatment, long duration LMWH resulted in fewer total PE (5 RCTs), but the summary OR was not statistically significant. Long duration LMWH resulted in statistically significantly lower risk of total DVT (6 RCTs) and proximal DVTs (5 RCTs). Data were insufficient for adverse events.

Key Question 4: Comparison of Single Versus Combination Classes in THR Studies

Key Points

- There were 7 RCTs and 2 NRCSs that compared single versus combined classes of intervention in patients undergoing THR.
- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE overall or avoid adverse events.

Summary Results

Note that network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5. However, in pairwise comparisons, relatively few studies directly compared combination versus single interventions (Table 28). Most specific comparisons were made by one study only.

For THR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus combination antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and antiplatelet drug, DTI, FXaI, and mechanical device; mechanical device alone versus the mechanical device and antiplatelet drug, both antiplatelet drug and UFH, and VKA; and UFH alone versus combination UFH and LMWH. In addition, one RCT compared combination antiplatelet drug and UFH versus combination antiplatelet device, UFH, and mechanical device.

Key Question 5: Network Meta-Analyses in THR Studies

Key Points

- Conclusions from all network meta-analyses are limited due to the sparseness of direct comparisons between most interventions within each network.
- Network meta-analyses that included more than sparse connections could be constructed for only total DVT and major bleeding. Other outcomes were too sparsely populated to allow interpretable networks.
- Findings were consistent with direct, pairwise comparisons of interventions to lower the risk of total DVT and major bleeding.
- Within network meta-analyses, the exact ranking of interventions is susceptible to change with the addition of more studies and the ranking orders are not supported by evaluations of statistical significance.
- Network meta-analysis suggests that
    - **By class**
        - Among 53 RCTs, FXaI and DTI are most likely to be most effective to prevent **total DVT;** mechanical devices, LMWH, VKA, and UFH are less effective (moderate SoE). Other intervention classes have too sparse evidence to provide sufficient conclusions.
        - Among 32 RCTs, LMWH is more likely to result in fewer **major bleeding** events than FXaI (low SoE). Other intervention classes have too sparse evidence to provide sufficient conclusions.

- **By intervention**
    - Among 54 RCTs, dalteparin is most likely to be most effective to prevent **total DVT**, compared with enoxaparin, IPC, UFH, and, warfarin (moderate SoE). Other interventions have too sparse evidence to provide sufficient conclusions.
    - Despite 34 RCTs, comparisons between specific pairs of interventions were too sparse to yield sufficient conclusions regarding risk of **major bleeding**.

Network meta-analysis findings are summarized in Table 28.

Total DVT: Comparison of Classes in THR Studies

There were 53 RCTs that evaluated interventions in at least two classes and reported total DVT after THR. Across this study set, 10 classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 45 possible pairwise comparisons, 17 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with seven other intervention classes, most frequently with FXaI (11 RCTs), UFH (10 RCTs), and placebo (12 RCTs). Antiplatelet drug was directly compared with placebo and VKA only; FEI was directly compared with FXaI only.

Overall, the combination of LMWH plus mechanical device intervention had the highest probability of being among the top three intervention classes (99%) to prevent total DVT in patients undergoing THR, followed by FXaI (64%). The interventions likely to be among the bottom three interventions were placebo (>99%), UFH (86%), and VKA (80%) However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (antiplatelet drug, FEI, and combined LMWH and mechanical devices), FXaI is most effective to prevent total DVT, followed by DTI, compared with mechanical devices, LMWH, VKA, and UFH.

DVT: Comparison of Specific Interventions in THR Studies

In the analysis by drug (or mechanical device), there were 54 RCTs that evaluated at least two interventions and reported total DVT after THR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included. Across this study set, 20 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, VFP, warfarin, placebo). Of the 190 possible pairwise comparisons, 33 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 14 other interventions; most frequently with UFH (7 RCTs) and placebo (8 RCTs). Dalteparin was directly compared with UFH, warfarin, and placebo only; warfarin was also directly compared with aspirin and IPC; aspirin was directly compared with placebo; TB402 was directly compared with rivaroxaban only.

Overall, the combination of enoxaparin plus IPC had the highest probability of being among the top three interventions to prevent DVT after THR (96%), followed by apixaban (67%). The interventions likely to be among the bottom three interventions were placebo (97%) and warfarin (58%) However, omitting interventions that are directly linked to two or fewer other

interventions with two or fewer RCTs each (most interventions), dalteparin is most effective to prevent total DVTs, compared with enoxaparin, IPC, UFH, and warfarin.

Major Bleeding: Comparison of Classes in THR Studies

There were 32 RCTs that evaluated interventions in at least two classes and reported major bleeding after THR. Across this study set, 9 classes were evaluated (antiplatelet drug [aspirin], DTI, FEI, FXaI, LMWH, mechanical devices, UFH, VKA, placebo). Of the 36 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with six other intervention classes; most frequently with FXaI (11 RCTs), UFH (6 RCTs) and placebo (6 RCTs). Antiplatelet drug was directly compared with placebo only; FEI was directly compared with FXaI only.

Overall, the mechanical devices had the highest probability of being among the top three intervention classes (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by VKA (89%) and VKA (78%). The interventions likely to be among the bottom three interventions were FEI (>99%) and UFH (88%). However, omitting interventions that are directly linked to two or fewer other interventions with two or fewer RCTs each (all classes except LMWH and FXaI—and placebo), LMWH was more likely to result in fewer major bleeding events than FXaI.

Major Bleeding: Comparison of Specific Interventions in THR Studies

In the analysis by drug (or mechanical device), there were 34 RCTs that evaluated at least two interventions and reported major bleeding after THR. Across this study set, 17 interventions were evaluated (apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, UFH, IPC, rivaroxaban, semuloparin, TB402, tinzaparin, warfarin, placebo). Of the 136 possible pairwise comparisons, 23 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 13 other interventions; most frequently with UFH (5 RCTs) and placebo (6 RCTs). Dalteparin was directly compared with UFH, warfarin, and edoxaban only; aspirin was directly compared with placebo only; TB402 was directly compared with rivaroxaban only.

Overall, IPC had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after THR, followed by semuloparin (63%). The interventions likely to be among the bottom three interventions were TB402 (>99%) and aspirin (86%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Key Question 6: Thromboprophylaxis Timing in THR Studies

Only two RCTs compared LMWH started at different times relative to THR surgery (Table 28). There was insufficient evidence to yield conclusions.

Table 28. Evidence profile for total hip replacement surgery

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
1 (Class vs. class, direct comparisons)	LMWH vs. DTI	DVT, total	RCT: 3 (4600)	Low	Consistent	Imprecise	Undetected	None	Favors DTI: range 1.14 to 1.52	Moderate
		DVT, proximal	RCT: 3 (4600)	Low	Consistent	Imprecise	Undetected	None	Favors DTI: range 1.35 to 1.89	Moderate
		Bleeding, major	RCT: 4 (6900)	Low	Consistent	Imprecise	Undetected	None	Favors LMWH: 0.79 (0.55, 1.14)	Low
		Mortality, 30 day or in-hospital	RCT: 3 (4600)	Low	Consistent	Highly imprecise	Undetected	None	Unclear: range 0.14 to 3.03	Insufficient
		VTE vs. AE[C] (reported)	*RCT: 4 (6900)*						*Tradeoff: Favors DTI to prevent DVT. Favors LMWH to minimize major bleeding.*	
	LMWH vs. FXaI	VTE, total	RCT: 6 (5801)	Medium[D]	Inconsistent	Precise	Suspected[E,F]	None	Favors FXaI: 2.18 (1.52, 3.13)	Low
		VTE, symptomatic	RCT: 7 (6157)	Medium[D]	Consistent	Imprecise	Suspected[E,F]	None	Favors LMWH: 0.72 (0.40, 1.30)	Low
		PE, total	RCT: 4 (10080)[G] NRCS: 1 (1056)	RCT: Low NRCS: High	Inconsistent	Highly Imprecise	Suspected[E]	None	Unclear: range 0.33 to 1.67	Insufficient
		PE, fatal	RCT: 9 (11564)[G]	Medium[D]	Unknown	Highly imprecise	Suspected[E]	Rare events	Unclear	Insufficient
		PE, symptomatic	RCT: 5 (1468)[G]	Medium[D]	Unknown	Highly imprecise	Suspected[E]	Rare events	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		DVT, total	RCT: 10 (9346) NRCS: 1 (1056)	RCT: Medium[D] NRCS: High	RCT: Inconsistent	RCT: Precise	Undetected	None	RCT: Favors FXaI: 1.71 (1.22, 2.39) NRCS: Either	Moderate
		DVT, symptomatic	RCT: 9 (11,954)	Medium[D]	Inconsistent	Imprecise	Suspected[E]	None	Favors LMWH: 0.76 (0.37, 1.57)	Low
		DVT, proximal	RCT: 10 (9622)	Medium[D]	Inconsistent	Precise	Undetected	None	Favors FXaI: 2.40 (1.23, 4.69)	Moderate
		Bleeding, major	RCT: 10 (12,457)	Medium[D]	Consistent	Precise	Undetected	None	Favors LMWH: 0.74 (0.54, 0.99)	High
		Bleeding, fatal	RCT: 3 (8900)	Low	Consistent	Highly imprecise	Undetected	No events	Unclear	Insufficient
		Bleeding → reoperation	RCT: 3 (8900)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient
		Bleeding, joint	RCT: 3 (8900)	Low	Inconsistent	Highly imprecise	Undetected	Rare events	Unclear: range 0.50 to 0.89	Insufficient
		Mortality, 30 day	RCT: 6 (10915)[G]	Low	Inconsistent	Highly imprecise	Undetected	Rare events	Unclear	Insufficient
		Serious adverse events (study-defined)	RCT: 5 (6727)	Medium[D]	Consistent	Precise	Suspected[E]	None	Either: 0.95 (0.78, 1.17)	Moderate
		VTE vs. AE[C] (reported)	*RCT: 13 (13,173)*						*Unclear: Inconsistent findings across VTE outcomes, but favors LMWH to minimize major bleeding.*	
	LMWH vs. Mechanical Devices	DVT, total	RCT: 3 (732)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		DVT, proximal	RCT: 3 (732)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient
	LMWH vs. UFH	PE, total	RCT: 8 (1878)	Low	Consistent	Precise	Undetected	None	Favors LMWH: 0.29 (0.13, 0.63)	High
		PE, fatal	RCT: 7 (1711)[G]	Low	Consistent	Highly imprecise	Suspected[E]	No events	Unclear	Insufficient
		DVT, total	RCT: 10 (2219)	Low	Consistent	Imprecise	Undetected	None	Either: 0.84 (0.60, 1.18)	Moderate
		DVT, symptomatic	RCT: 4 (488)	Low	Consistent	Highly imprecise	Suspected[E]	None	Unclear: 0.83 (0.30, 2.35)	Insufficient
		DVT, proximal	RCT: 6 (1506)	Low	Consistent	Precise	Suspected[E]	None	Favors LMWH: 0.59 (0.38, 0.93)	Moderate
		Bleeding, major	RCT: 6 (1960)	Low	Consistent	Precise	Suspected[E]	None	Favors LMWH: 0.46 (0.23, 0.92)	Moderate
		Bleeding, fatal	RCT: 6 (1308)[G]	Low	Consistent	Highly imprecise	Undetected	No events	Unclear	Insufficient
		Mortality, 30-day or in-hospital	RCT: 6 (1640)[G]	Low	Consistent	Highly imprecise	Undetected	Rare events	Unclear	Insufficient
		Heparin-induced thrombo-cytopenia	RCT: 3 (1163)	Low	Consistent	Highly imprecise	Undetected	Rare events	Unclear	Insufficient
		VTE vs. AE[C] (reported)	*RCT: 10 (2387)*						*Favors LMWH: Lower risk VTE outcomes and major bleeding.*	
	LMWH vs. VKA	PE, total	RCT: 3 (4537)	Low	Consistent	Highly imprecise	Undetected	Rare events	Unclear	Insufficient
		PE fatal	RCT: 3 (4537)	Low	Consistent	Highly imprecise	Undetected	Rare events	Unclear	Insufficient
		DVT, total	RCT: 3 (4537)	Low	Inconsistent	Imprecise	Undetected	None	Unclear: range 0.48 to 0.87	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		DVT, proximal	RCT: 3 (4537)	Low	Inconsistent	Highly imprecise	Undetected	None	Unclear: range 0.27 to 1.27	Insufficient
		Bleeding, major	RCT: 4 (5332)	Low	Consistent	Precise	Undetected	None	Favors VKA: 1.96 (1.14, 3.38)	High
	LMWH vs. antiplatelet (ASA) drug	PE, total	NRCS: 2 (110,117)[H]	Low	Inconsistent	Precise	Undetected	Sparse, Large NRCS	Either: 0.94 (0.75, 1.17)	Low
		DVT, symptomatic	NRCS: 1 (108,584)[H]	Low	N/A	Imprecise	Undetected	Sparse, Large NRCS	Either: 0.84 (0.70, 1.03)	Low
		Bleeding, major	NRCS: 1 (108,584)[H]	Low	N/A	Precise	Undetected	Sparse, Large NRCS	Either: 0.95 (0.77, 1.17)	Low
		VTE vs. AE[C] (reported)	NRCS: 2 (110,117)				Undetected		Either: Similar VTE outcomes and major bleeding with LMWH and aspirin.	
	Mechanical Devices vs. VKA	DVT, total	RCT: 3 (434)	Low	Inconsistent	Imprecise	Undetected	None	Unclear: range 0.18 to 1.00	Insufficient
		DVT, proximal	RCT: 3 (434)	Low	Consistent	Precise	Undetected	None	Favors VKA: range 2.39 to 4.69	High
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different doses)	FXaI low vs. high dose	VTE, total	RCT: 4 (981)	High[I]	Inconsistent	Precise	Undetected	None	Favors high dose: 1.55 (0.78, 3.06)	Low
	LMWH low vs. high dose	DVT, total	RCT: 5 (1441)	Medium[D]	Inconsistent	Imprecise	Undetected	None	Favors high dose: 1.33 (0.56, 3.18)	Low
		DVT, proximal	RCT: 4 (1047)	Medium[D]	Consistent	Highly imprecise	Undetected	None	Either:1.04 (0.55, 1.98)	Low

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		Bleeding, major	RCT: 4 (1498)	Medium[D]	Consistent	Precise	Undetected	None	Favors low dose: 0.42 (0.21 to 0.86)	Moderate
		VTE vs. AE[C] (reported)	*RCT: 5 (1580)*						*Tradeoff: Favors higher dose to prevent total DVT. Favors lower dose to minimize major bleeding.*	
	Other comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different durations)	LMWH short vs. long duration	PE, total	RCT: 5 (1128)	Low	Consistent	Imprecise	Undetected	None	Favors long duration: 2.35 (0.83, 6.62)	Low
		PE, fatal	RCT: 4 (1087)[G]	Low	Consistent	Highly imprecise	Suspected[E]	Rare events	Unclear	Insufficient
		DVT, total	RCT: 6 (1463)	Low	Consistent	Precise	Undetected	None	Favors long duration: 2.87 (2.08, 3.96)	High
		DVT, symptomatic	RCT: 3 (1258)	Low	Inconsistent	Highly imprecise	Suspected[E]	None	Unclear: range 0.53 to 4.20	Insufficient
		DVT, proximal	RCT: 5 (1300)	Low	Consistent	Precise	Suspected[E]	None	Favors long duration: 2.94 (1.62, 5.35)	Moderate
		Bleeding, major	RCT: 3 (895)	Low	Consistent	Highly imprecise	Suspected[E]	None	Unclear	Insufficient
		Bleeding, fatal	RCT: 4 (1135)[G]	Low	Consistent	Highly imprecise	Undetected	No events	Unclear	Insufficient
		Mortality, 30 day	RCT: 3 (873)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient
	Other comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
4 (Single vs. combination classes)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
5 (Ranking of class vs. class, per NMA)	All classes[iJ]	DVT, total	RCT: 53	Low[K]	Consistent[K]	Precise[iK]	Undetected[K]	Few direct comparisons	FXaI and DTI most effective[L] Mechanical devices and LMWH middle effectiveness[L] UFH and VKA least effective[L]	Moderate
		Bleeding, major	RCT: 32	Low[K]	Consistent[K]	Precise[K]	Suspected[E,K]	Very few direct comparisons	Favors LMWH over FXaI[L]	Low
5 (Ranking of intervention vs. intervention, per NMA)	All interventions[M]	DVT, total	RCT: 54	Low[K]	Consistent[K]	Precise[K]	Undetected[K]	Few direct comparisons	Favors dalteparin > enoxaparin > IPC > UFH > warfarin[L]	Moderate
		Bleeding, major	RCT: 34	Low[K]	Consistent[K]	Imprecise[K]	Suspected[E,K]	Sparse direct comparisons	Unclear	Insufficient
6 (Different start times)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse events; CI = confidence interval, DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, IPC = intermittent pneumatic compression devices, LMWH = low molecular weight heparin, NMA = network meta-analysis, NRCS = nonrandomized comparative study, OR = odds ratio, PE = pulmonary embolism, RCT = randomized controlled trials, UFH = unfractionated heparin, VKA = vitamin K inhibitor.

[A] Evaluated outcomes included total VTE, symptomatic VTE, total PE, fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events. For each comparison, omitted outcomes had insufficient data with two or fewer studies.

[B] "Unclear" should be interpreted as no evidence of a difference (in contrast to evidence of no difference).

[C] Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

[D] High risk of bias in 1 or 2 of 5 or more RCTs.
[E] <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias).
[F] Different trials reported either total VTE or symptomatic VTE resulting in conflicting findings between the two outcomes (FXaI results in fewer total VTE, but LMWH results in fewer symptomatic VTE).
[G] Fewer than 4 RCTs per comparison for individual outcome were analyzable, because other RCTs had no events.
[H] Although ≤2 studies, one is a very large nonrandomized comparative study that used propensity score analysis. A *post hoc* determination was made that this allowed for low strength of evidence.[I] High risk of bias in 2 of 4 RCTs.
[J] Antiplatelet drug, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical devices, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical devices.
[K] Among classes (or interventions) compared to at least two other classes (or interventions) by at least 2 trials.
[L] Among the described interventions. Too few RCTs evaluated other interventions, which resulted in insufficient evidence.
[M] Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, unfractionated heparin, intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.

Total Knee Replacement

Across Key Questions, 60 eligible studies evaluated thromboprophylaxis interventions in patients who underwent TKR. The largest number compared different classes of interventions (relevant to Key Questions 1 and 5). The most commonly evaluated intervention class was LMWH, mostly in comparison with DTI, FXaI, and VKA. Other interventions were relatively infrequently evaluated in comparative effectiveness trials (i.e., comparisons of active, nonplacebo interventions). The most commonly evaluated outcomes were total DVT and major bleeding. SoE is summarized in Table 29.

Key Question 1: Comparison of Intervention Classes in TKR Studies

Note that network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- There were 29 RCTs and 6 NRCSs that compared classes of interventions in patients undergoing TKR.
- Pairwise comparisons between classes had sufficient data for meta-analyses for only two pairs of classes.
    - **LMWH vs. FXaI**: Overall, the evidence is unclear. FXaI results in a lower risk of total VTE (low SoE), total DVT (low SoE), and proximal DVT (moderate SoE), but similar risks for total VTE (moderate SoE) and symptomatic DVT (low SoE); risk of major bleeding is lower with LMWH (low SoE) but risk of study-defined serious adverse events is lower with FXaI (low SoE).
    - **LMWH vs. VKA**: There is a tradeoff in risks between the two drug classes, such that LMWH better lowers risk of total DVT (high SoE) and proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE).
    - For all other class comparisons and outcomes there was insufficient direct comparative evidence.
    - Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events; most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.

- A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug vs. mechanical device between unilateral or bilateral TKR surgery.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results

Pairwise comparisons between classes had sufficient data for meta-analysis for only two pairs of classes (Table 29). For the comparison of LMWH versus FXaI, across 10 RCTs, meta-analysis significantly favored FXaI to prevent total DVT (7 RCTs) and proximal DVT (6 RCTs). While not statistically significant, the evidence favored FXaI to reduce the risk of total VTE (4 RCTs) with lower rates of study-defined serious adverse events (4 RCTs). Major bleeding occurred (nonsignificantly) less frequently with LMWH (7 RCTs). Rates of symptomatic DVT were the same with both drug classes (8 RCTs).

Among 4 RCTs that compared LMWH versus VKA, LMWH treatment resulted in less frequent total DVT (nonsignificantly) in 3 RCTs and proximal DVT across 4 RCTs (also not statistically significant); 4 RCTs found (nonsignificantly) lower risk of major bleeding with VKA.

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drug (aspirin) versus FXaI (1 RCT), antiplatelet drug versus mechanical devices (1 RCT, 1 NRCS), antiplatelet drug versus VKA (1 RCT), DTI versus FXaI (1 RCT), LMWH versus antiplatelet drug (1 RCT), LMWH versus FXIi (1 RCT), LMWH versus mechanical devices (1 RCT and 1 NRCS), LMWH versus UFH (2 RCTs), and VKA versus mechanical devices (1 NRCS). Five RCTs evaluated LMWH vs. DTI but had highly inconsistent findings related to symptomatic DVT (3 RCTs) and rare episodes of major bleeding resulting in a highly imprecise effect estimate (5 RCTs).

Subgroup Analysis

One RCT compared subgroups of patients who received unilateral or bilateral TKR surgery in a comparison of antiplatelet drug (aspirin) versus mechanical device; the trial was conducted in the 1980s and included an unrestricted sample of adult patients undergoing TKR. They found that in the unilateral surgery group (n=72) the percent of patients with a DVT was lower for those receiving mechanical prophylaxis through a compression boot (22%) compared to those receiving aspirin (47%, P<0.03). In the bilateral surgery group (n=47), DVT incidence was also lower in patients who used compression boots (48%) compared with those who received aspirin (68%), but this difference was not significant (P<0.20). Whether the treatment effect differed between unilateral and bilateral surgery subgroups was not analyzed.

Studies were generally homogeneous in terms of patient eligibility criteria, such that most across-study comparisons of subgroup factors are limited.

Among TKR RCTs, differences between studies based on industry funding was analyzable for only the comparison of LMWH versus FXaI. For total DVT, by random effects model metaregression no significant difference (P=0.21) was found between the six industry-funded studies (summary OR 2.04, 95% CI 1.68 to 2.49) and the single study without industry support (OR 4.71, 95% CI 1.31 to 16.9).

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies

(summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregression. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Key Question 2: Comparison of Within-Class Interventions in TKR Studies

Note that network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Relatively few RCTs of thromboprophylaxis compared specific interventions within any given class (2 for TKR) (Table 29). No comparison was evaluated by more than two studies. In patients undergoing TKR, one or two RCTs each evaluated enoxaparin versus semuloparin (LMWHs), enoxaparin versus tinzaparin (LMWHs), and graduated compression stockings versus intermittent pressure devices (mechanical devices). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations in TKR Studies

Key Points

- There were 18 RCTs and 1 NRCS that compared different intervention doses or durations in patients undergoing TKR.
  - **DTI low vs. high dose**: There is evidence of a tradeoff between low and high dose DTI. Higher dose DTI (dabigatran 220 to 225 mg) has a lower risk of total DVT (high SoE) and proximal DVT (moderate SoE) than lower dose (dabigatran 150 mg), but lower dose DTI has less risk of major bleeding (low SoE)
  - **FXaI low vs. high dose**: Overall, the evidence is unclear. Higher dose FXaI (e.g., edoxaban 60 mg, darexaban 30 mg) results in a lower risk of total VTE (moderate SoE), symptomatic DVT (low SoE), and proximal DVT (low SoE) than lower dose FXaI (e.g., edoxaban 5 mg, darexaban 15 mg); however, there was insufficient evidence for adverse events.

Summary Results

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level analyses; specific intervention comparisons were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

For only two pairwise comparisons of dose or treatment duration were there sufficient data (Table 29). Among five RCTs of low versus high dose DTI, studies favored higher dose DTI (e.g., dabigatran 220 mg/day) over lower dose DTI (e.g., dabigatran 150 mg/day) to prevent total DVT (3 RCTs) and proximal DVT (4 RCTs). By meta-analysis the five RCTs nonsignificantly favored lower dose DTI to avoid major bleeding.

Among four RCTs of low versus high dose FXaI, studies favored higher dose FXaI (multiple drugs, mostly twice the lower dose) over lower dose FXaI to prevent total VTE (4 RCTs), symptomatic DVT (4 RCTs), and proximal DVT (4 RCTs). Four RCTs were highly imprecise and inconsistent regarding difference in major bleeding risk, thus providing insufficient evidence.

Key Question 4: Comparison of Single Versus Combination Classes in TKR Studies

Key Points

- There were 8 RCTs and 3 NRCSs that compared single versus combined classes of intervention in patients undergoing TKR.
- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE overall or avoid adverse events.

Summary Results

Note that network meta-analyses comparing individual interventions (including combination interventions) in regard to total DVT and major bleeds are presented under Key Question 5. However, in pairwise comparisons, relatively few studies directly compared combination versus single interventions (Table 29). Most specific comparisons were made by one study only.

For TKR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus combination antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and FEI or mechanical device, and UFH alone versus combination UFH and LMWH.

Key Question 5: Network Meta-Analyses in TKR Studies

Key Points

- Conclusions from all network meta-analyses are limited due to the sparseness of direct comparisons between most interventions within each network.
- Network meta-analyses that included more than sparse connections could be constructed for only total DVT and major bleeding. Other outcomes were too sparsely populated to allow interpretable networks.
- Network meta-analysis suggests that
  - **By class**
    - Among 31 RCTs, FXaI is more effective to prevent **total DVT** than LMWH (low SoE).
    - Among 23 RCTs, LMWH is more likely to result in fewer **major bleeding** events than FXaI (low SoE).
    - Other intervention classes have too sparse evidence to provide sufficient conclusions.
  - **By intervention**
    - Among 33 RCTs for **total DVT** and 24 RCTs for **major bleeding**., data were too sparse to yield sufficient conclusions.

Network meta-analysis findings are summarized in Table 29.

DVT: Comparison of Classes in TKR Studies

There were 31 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR. Across this study set, 12 classes were evaluated (antiplatelet drug [aspirin], antiplatelet drug plus mechanical device, DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 66 possible pairwise comparisons, 20 are covered by direct study comparisons. LMWH was the most common comparator, being directly compared with nine other intervention classes; most frequently with FXaI (7 RCTs). The combination of antiplatelet drug plus mechanical device was directly compared with antiplatelet drug and LMWH plus mechanical device; the combination of FXaI plus mechanical device was directly compared with FXaI only.

Overall, FXaI had the highest probability of being among the top three intervention classes (84%) to prevent DVT after TKR, followed closely by the combination of LMWH plus mechanical device (81%), then the combination of antiplatelet drug plus mechanical device (66%). The interventions likely to be among the bottom three interventions were placebo (>99%), antiplatelet drug (86%), and VKA (76%). However, except for LMWH and FXaI (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. FXaI is more effective to prevent total DVTs than LMWH.

DVT: Comparison of Specific Interventions in TKR Studies

In the analysis by drug (or mechanical device), there were 33 RCTs that evaluated at least two interventions and reported total DVT after TKR. However, one RCT of certoparin versus certoparin plus IPC did not connect to the network of evidence and was not included. Across this study set, 23 interventions were evaluated (apixaban, aspirin, aspirin plus IPC, aspirin plus VFP, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, enoxaparin plus GCS, enoxaparin plus IPC, enoxaparin plus VFP, flexion, fondaparinux, FXIASO, UFH, IPC, rivaroxaban, semuloparin, tinzaparin, VFP, warfarin, placebo). Of the 253 possible pairwise comparisons, 34 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with 16 other interventions. Flexion was directly compared with placebo only; enoxaparin plus GCS was directly compared with enoxaparin plus IPC only; IPC and aspirin plus VFP were directly compared with aspirin only; aspirin plus IPC was directly compared with enoxaparin plus IPC only; and edoxaban plus VFP was directly compared with edoxaban only.

Overall, rivaroxaban had the highest probability (68%) of being among the top three interventions to prevent DVT after TKR, followed by flexion (65%) and the combination of enoxaparin plus VFP (63%) and the combination of aspirin plus VFP (59%). The interventions likely to be among the bottom three interventions were the combination of enoxaparin plus GCS (>99%) and placebo (76%). However, except for enoxaparin (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each.

Major Bleeding: Comparison of Classes in TKR Studies

There were 23 RCTs that evaluated interventions in at least two classes and reported major bleeding after TKR. However, one RCT of antiplatelet drug (aspirin) versus the combination of antiplatelet drug (aspirin) plus mechanical device did not connect to the network of evidence and was not included. Across this study set, 8 classes were evaluated (DTI, FXaI, FXaI plus mechanical device, FXIi, LMWH, UFH, VKA, placebo). Of the 28 possible pairwise comparisons, 10 are covered by direct study comparisons. LMWH was the most common

comparator, being directly compared with each of six other intervention classes; most frequently with FXaI (7 RCTs), DTI (5 RCTs), and VKA (4 RCTs). The combination of FXaI plus mechanical device was directly compared to FXaI only.

Across all comparisons, there were no statistically significant differences. Overall, VKA had the highest probability of being among the top three intervention classes (84%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did not provide major bleeding data except for the one study of FXaI plus mechanical device versus FXaI. The interventions likely to be among the bottom three interventions were FXIi (68%) and FXaI (60%). However, except for LMWH (and placebo) no intervention was directly compared to more than two other interventions by at least two RCTs each. LMWH was more likely to result in fewer major bleeding events than FXaI.

Major Bleeding: Comparison of Specific Interventions in TKR Studies

In the analysis by drug (or mechanical device), there were 24 RCTs that evaluated at least two interventions and reported major bleeding after TKR. However, one RCT of aspirin versus the combination of aspirin plus VFP did not connect to the network of evidence and was not included. Across this study set, 15 interventions were evaluated (apixaban, dabigatran, darexaban, edoxaban, edoxaban plus VFP, enoxaparin, eribaxaban, fondaparinux, FXIASO, UFH, semuloparin, TAK422, tinzaparin, warfarin, placebo). Of the 105 possible pairwise comparisons, 22 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with each of 13 other interventions; most frequently with dabigatran (5 RCTs). The combination of edoxaban plus VFP was directly compared with edoxaban only.

Across all comparisons, there were no statistically significant differences. Overall, FXIASO had the highest probability of being among the top three interventions (67%) to avoid major bleeding with thromboprophylaxis after TKR. Notably, though the mechanical device RCTs did not provide major bleeding data except for one study of the combination of edoxaban plus VFP versus edoxaban. The interventions likely to be among the bottom three interventions were darexaban (96%) and fondaparinux (65%). However, except for enoxaparin no intervention was directly compared to more than two other interventions by at least two RCTs each.

Key Question 6: Thromboprophylaxis Timing in TKR Studies

No eligible studies evaluated patients with TKR (Table 29).

Table 29. Evidence profile for total knee replacement surgery

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
1 (Class vs. class, direct comparisons)	Antiplatelet vs. FXaI	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	Antiplatelet vs. Mechanical Device	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	Antiplatelet vs. VKA	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	DTI vs. FXaI	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. antiplatelet	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. DTI	DVT, symptomatic	RCT: 3 (2906)	Low	Inconsistent	Highly imprecise	Suspected[C]	None	Unclear: range 0.67 to 7.96	Insufficient
		Bleeding, major	RCT: 5 (3514)	Low	Consistent	Highly Imprecise	Undetected	None	Unclear: 0.96 (0.43, 2.16)	Insufficient
	LMWH vs. FXaI	VTE, total	RCT: 4 (1260)	Medium[D]	Consistent	Imprecise	Suspected[C]	None	Favors FXaI: 1.33 (0.89, 1.99)	Low
		VTE, symptomatic	RCT: 3 (2058)	Medium[D]	Inconsistent	Highly imprecise	Suspected[C]	None	Unclear: range 0.25 to 2.02	Insufficient
		PE, total	RCT: 5 (4693)[E]	Medium[D]	Consistent	Highly imprecise	Suspected[C]	Sparse	Unclear: range 0.14 to 2.59	Insufficient
		PE, fatal	RCT: 5 (5214)[E]	Medium[D]	Inconsistent	Highly imprecise	Suspected[C]	None	Unclear: range 0.20 to 1.00	Insufficient
		PE, symptomatic	RCT: 3 (121)	Medium[D]	Consistent	Highly imprecise	Suspected[C]	None	Unclear	Insufficient
		DVT, total	RCT: 7 (3805)	High[F]	Consistent	Precise	Suspected[C]	None	Favors FXaI: 2.09 (1.70, 2.58)	Low
		DVT, symptomatic	RCT: 8 (5715)	High[F]	Consistent	Imprecise	Undetected	None	Either: 0.99 (0.51, 1.91)	Low
		DVT, proximal	RCT: 6 (4402)	Medium[D]	Consistent	Precise	Suspected[C]	None	Favors FXaI: 1.84 (1.07, 3.16)	Moderate
		Bleeding, major	RCT: 7 (5926)	Medium[D]	Inconsistent	Imprecise	Suspected[C]	None	Favors LMWH: 0.74 (0.42, 1.30)	Low
		Mortality, 30 day	RCT: 3 (3189)	Medium[D]	Inconsistent	Highly imprecise	Undetected	None	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		Serious adverse events (study-defined)	RCT: 4 (1803)	Medium[D]	Consistent	Imprecise	Suspected[C]	None	Favors FXaI: 1.51 (0.80, 2.85)	Low
		VTE vs. AE[G] (reported)	*RCT: 10 (6350)*						*Unclear Favors FXaI to prevent VTE outcomes, but inconsistent regarding major bleeding and serious adverse events.*	
	LMWH vs. FXIi	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. Mechanical Device	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. UFH	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. VKA	PE, total	RCT: 4 (1878)	Low	Consistent	Highly imprecise	Undetected	None	Unclear: 0.61 (0.15, 2.43)	Insufficient
		PE, fatal	RCT: 3 (1742)	Low	Consistent	Highly imprecise	Undetected	No events	Unclear	Insufficient
		DVT, total	RCT: 3 (1742)	Low	Consistent	Precise	Undetected	None	Favors LMWH: range 0.42 to 0.67	High
		DVT, proximal	RCT: 4 (1772)	Low	Inconsistent	Imprecise	Undetected	None	Favors LMWH: 0.51 (0.21, 1.28)	Low
		Bleeding, major	RCT: 4 (1960)[E]	Low	Consistent	Imprecise	Undetected	None	Favors VKA: range 1.16 to 3.13	Low
		Bleeding, fatal	RCT: 3 (1742)	Low	Consistent	Highly imprecise	Undetected	Sparse	Unclear	Insufficient
		VTE vs. AE[G] (reported)	*RCT: 4 (1960)*						*Tradeoff: Favors LMWH to prevent DVT. Favors VKA to minimize major bleeding.*	
	VKA vs. FXaI	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different doses)	DTI low vs. high dose	DVT, total	RCT: 3 (577)	Medium[D]	Consistent	Precise	Undetected	None	Favors high dose; range: 1.54 to 2.08	High
		DVT, symptomatic	RCT: 4 (3141)	Medium[D]	Consistent	Highly imprecise	Undetected	None	Unclear: 1.14 (0.49, 2.65)	Insufficient
		DVT, proximal	RCT: 4 (1860)	Medium[D]	Consistent	Precise	Undetected	None	Favors high dose: 1.57 (0.83, 2.96)	Moderate
		Bleeding, major	RCT: 5 (3875)	Medium[D]	Consistent	Imprecise	Undetected	None	Favors low dose: 0.65 (0.34, 1.24)	Low
		Mortality, 30 day or in-hospital	RCT: 4 (3628)[E]	Medium[D]	Inconsistent	Imprecise	Undetected	Sparse	Unclear	Insufficient
		VTE vs. AE[G] *(reported)*	RCT: 5 (3875)						Tradeoff: Favors higher dose to prevent DVT. Favors lower dose to minimize major bleeding.	
	FXaI low vs. high dose	VTE, total	RCT: 4 (779)	High[H]	Consistent	Precise	Undetected	None	Favors high dose: 2.06 (1.48, 2.86)	Moderate
		DVT, symptomatic	RCT: 4 (802)	High[H]	Consistent	Precise	Undetected	Sparse	Favors high dose: range: 2.93 to 4.37	Low
		DVT, proximal	RCT: 4 (784)	High[H]	Consistent	Imprecise	Undetected	None	Favors high dose: 2.51 (0.85, 7.42)	Low
		Bleeding, major	RCT: 4 (1095)	High[H]	Consistent	Highly imprecise	Undetected	Sparse	Either: range: 0.32 to 5.03	Insufficient
	Dabigatran 150 mg vs. 220 mg	DVT, symptomatic	RCT: 3 (2879)	Low	Inconsistent	Highly imprecise	Undetected	None	Unclear	Insufficient
		Bleeding, major	RCT: 3 (3365)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient

Key Question	Intervention(s)	Outcome[A]	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings[B] — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
		Bleeding, fatal	RCT: 3 (3365)	Low	Consistent	Highly imprecise	Undetected	No events	Unclear	Insufficient
		Bleeding → reoperation	RCT: 3 (3365)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient
		Mortality, 30 day	RCT: 3 (3365)	Low	Consistent	Highly imprecise	Undetected	None	Unclear	Insufficient
	Other comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different durations)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
4 (Single vs. combination classes)	LMWH vs. LMWH+Mechanical Device	DVT, total	RCT: 3					Sparse	Unclear	Insufficient
	All other comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
5 (Ranking of class vs. class, per NMA)	All classes[I]	DVT, total	RCT: 31	Low[J]	Consistent[J]	Precise[J]	Undetected[J]	Very few direct comparisons	Favors FXaI over LMWH[J]	Low
		Bleeding, major	RCT: 23	Low[J]	Consistent[J]	Precise[J]	Suspected[C,J]	Very few direct comparisons	Favors LMWH over FXaI[J]	Low
5 (Ranking of intervention vs. intervention, per NMA)	All interventions[K]	DVT, total	RCT: 33	Low[J]	Consistent[J]	Imprecise[J]	Undetected[J]	Sparse direct comparisons	Unclear	Insufficient
		Bleeding, major	RCT: 24	Low[J]	Consistent[J]	Imprecise[J]	Suspected[C,J]	Sparse direct comparisons	Unclear	Insufficient
6 (Different start times)	All comparisons	All outcomes	RCT: 0					Sparse	Unclear	Insufficient

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Italicized rows summarize across both venothromboembolism (VTE) outcomes and adverse events (for which there are sufficient evidence). Other abbreviations: AE = adverse

events, CI = confidence interval, DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, NMA = network meta-analysis, NRCS = nonrandomized comparative study, OR = odds ratio, PE = pulmonary embolism, RCT = randomized controlled trials, UFH = unfractionated heparin, VKA = vitamin K inhibitor.

[A] Evaluated outcomes included total VTE, symptomatic VTE, total PE, fatal PE, symptomatic PE, total DVT, symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events. For each comparison, omitted outcomes had insufficient data with two or fewer studies.

[B] "Unclear" should be interpreted as no evidence of a difference (in contrast to evidence of no difference).

[C] <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias).

[D] High risk of bias in 1 or 2 of 5 or more RCTs.

[E] Fewer than 4 RCTs per comparison for individual outcome were analyzable, because other RCTs had no events.

[F] High risk of bias in 3 RCTs.

[G] Comparison of reported outcomes with sufficient evidence (i.e., not graded "insufficient" SoE). This row omitted if there is sufficient evidence for only VTE outcomes (not for adverse events) or only for adverse events (not for VTE outcomes).

[H] High risk of bias in 2 of 4 RCTs.[I] Antiplatelet drug, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical devices, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical device.

[J] Among classes (or interventions) compared to at least two other classes (or interventions) by at least 2 trials.

[K] Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin (unfractionated), intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.

Hip Fracture Surgery

Across Key Questions, 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. No comparison between classes, interventions, or intervention regimens was evaluated by more than three studies, mostly by only one RCT. SoE is insufficient throughout and summarized in Table 30.

Key Question 1: Comparison of Intervention Classes in HFx Surgery Studies

Note that network meta-analyses comparing classes in regard to total DVT and major bleeds are presented under Key Question 5. The results of comparisons with what was deemed to have sufficient evidence are summarized here; other comparisons are noted, but were deemed to have insufficient evidence.

Key Points

- There were 6 RCTs that compared classes of interventions in patients undergoing HFx surgery.
- **LMWH vs. FXaI**: Overall, the evidence is unclear. There is moderate SoE that LMWH results in a lower risk of total DVT. There is insufficient evidence for all other outcomes, including adverse events.

Summary Results

Only 6 RCTs of thromboprophylaxis have been conducted comparing intervention classes in patients undergoing HFx surgery. Pairwise comparisons between classes had sufficient data only for the comparison of LMWH versus FXaI (Table 30). The 3 RCTs that compared LMWH versus FXaI found lower risk of total DVT with LMWH, but there was insufficient evidence regarding other outcomes. Other interventions classes compared included antiplatelet drug

(aspirin) versus mechanical devices (1 RCT), antiplatelet drug versus VKA (1 RCT), and LMWH versus UFH (1 RCT); there was insufficient evidence regarding these comparisons.

Key Question 2: Comparison of Within-Class Interventions in HFx Surgery Studies

Note that network meta-analyses comparing individual interventions in regard to total DVT and major bleeds are presented under Key Question 5.

Only two RCTs compared specific interventions within any given class for patients undergoing HFx surgery (Table 30). In patients with HFx surgery, one RCT each compared enoxaparin versus dalteparin (LMWHs) and enoxaparin versus semuloparin (LMWHs). Evidence was insufficient to evaluate within-class intervention comparisons.

Key Question 3: Comparison of Dosages and Treatment Durations in HFx Surgery Studies

One RCT each compared different duration FXaI and LMWH, providing insufficient evidence (Table 30).

Key Question 4: Comparison of Single Versus Combination Classes in HFx Surgery Studies

No studies compared single class and combination class interventions after HFx surgery (Table 30).

Key Question 5: Network Meta-Analyses in HFx Surgery Studies

Key Points

- Conclusions from all network meta-analyses are limited due to the sparseness of direct comparisons between most interventions within each network.
- Network meta-analyses that included more than sparse connections could be constructed for only total DVT and major bleeding. Other outcomes were too sparsely populated to allow interpretable networks.
- Comparisons between specific pairs of classes or of interventions were too sparse to yield sufficient conclusions regarding risks of total DVT or major bleeding.
    - There were 6 RCTs that compared classes of interventions for total DVT and 21 compared classes of interventions for major bleeding; 8 RCTs compared specific interventions for total DVT and 6 for major bleeding.

Network meta-analysis findings are summarized in Table 30.

DVT: Comparison of Classes in HFx Surgery Studies

There were six RCTs that evaluated interventions in at least two classes and reported total DVT after HFx surgery. However, one RCT of antiplatelet drug (aspirin) versus mechanical device did not connect to the network of evidence. Across this study set, four classes were evaluated (FXaI, LMWH, UFH, placebo). Of the six possible pairwise comparisons, four are covered by direct study comparisons. LMWH was directly compared with each of the three other intervention classes; FXaI was also directly compared with placebo.

There were no statistically significant differences. Overall, FXaI and UFH were likely to be

among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

DVT: Comparison of Specific Interventions in HFx Surgery Studies

In the analysis by drug (or mechanical device), there were eight RCTs that evaluated at least two interventions and reported total DVT after HFx surgery. One RCT of aspirin versus VFP did not connect to the network of evidence. Across this study set, seven interventions were evaluated (dalteparin, edoxaban, enoxaparin, fondaparinux, UFH, semuloparin, placebo). Of the 21 possible pairwise comparisons, 8 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. UFH was directly compared with dalteparin only.

Overall, UFH had the highest probability of being among the top three interventions to prevent DVT after HFx surgery (95%), followed by fondaparinux (89%) and dalteparin (70%). The other three interventions were likely to be among the bottom three interventions: placebo (92%), enoxaparin (79%), and edoxaban (79%) However, no intervention was directly compared to two other interventions by at least two RCTs.

Major Bleeding: Comparison of Classes in HFx Surgery Studies

There were four RCTs that evaluated interventions in at least two classes and reported major bleeding after HFx surgery. Across this study set, five classes were evaluated (antiplatelet drug [aspirin], FXaI, LMWH, VKA, placebo). Of the 10 possible pairwise comparisons, 6 are covered by direct study comparisons. Placebo was the most common comparator, being directly compared with each of the five other intervention classes.

There were no statistically significant differences. Overall, antiplatelet drug had the highest probability of being among the top two interventions (96%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by VKA (52%). The interventions likely to be among the bottom two interventions were FXaI (98%) and LMWH (96%). However, except for the comparison of LMWH and FXaI, only single RCTs compared intervention classes.

Major Bleeding: Comparison of Specific Interventions in HFx Surgery Studies

In the analysis by drug (or mechanical device), there were six RCTs that evaluated at least two interventions and reported major bleeding after HFx surgery. Across this study set, eight interventions were evaluated (aspirin, dalteparin, edoxaban, enoxaparin, fondaparinux, semuloparin, warfarin, and placebo). Of the 28 possible pairwise comparisons, 9 are covered by direct study comparisons. Enoxaparin was the most common comparator, being directly compared with five other interventions. Aspirin and warfarin were directly compared with each other and placebo only.

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding with thromboprophylaxis after HFx surgery, followed by placebo (95%) and warfarin (94%). The interventions likely to be among the bottom three interventions were fondaparinux (82%), semuloparin (77%), and enoxaparin (67%). However, only enoxaparin and fondaparinux were directly compared by two RCTs, with similar risk of major bleeding.

Key Question 6: Thromboprophylaxis Timing in HFx Surgery Studies

No eligible studies evaluated patients with HFx surgery (Table 30).

Table 30. Evidence profile for hip fracture surgery

Key Question	Intervention(s)	Outcome*	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings† — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
1 (Class vs. class, direct comparisons)	Antiplatelet vs. Mechanical Device	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	Antiplatelet vs. VKA	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
	LMWH vs. FXaI	DVT, total	RCT: 3 (1816)	Low	Inconsistent	Precise	Undetected	None	Favors LMWH: 2.71 to 3.81‡	Moderate
		Bleeding, major	RCT: 3 (1816)	Low	Inconsistent	Highly imprecise	Undetected	None	Unclear: range 0.18 to 2.09	Insufficient
	LMWH vs. UFH	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
2 (Intervention vs. intervention, direct comparisons)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different doses)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
3 (Different durations)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
4 (Single vs. combination classes)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient
5 (Ranking of class vs. class, per NMA)	All classes‖	DVT, total	RCT: 5 (2003)	Low	Consistent	Imprecise	Undetected	Sparse direct comparisons	Unclear	Insufficient
		Major bleeding	RCT: 4 (2039)	Low	Consistent	Imprecise	Suspected §	Sparse direct comparisons	Unclear	Insufficient
5 (Ranking of intervention vs. intervention, per NMA)	All interventions#	DVT, total	RCT: 8 (3122)	Low	Consistent	Imprecise	Undetected	Sparse direct comparisons	Unclear	Insufficient
		Major bleeding	RCT: 6 (3158)	Low	Consistent	Imprecise	Suspected §	Sparse direct comparisons	Unclear	Insufficient

Key Question	Intervention(s)	Outcome*	Design: No. Studies (N)	Study Limitations	Consistency	Precision	Reporting Bias	Other Issues	Findings† — Favors: Summary OR (95% CI) or Range of Estimates	SoE Grade
6 (Different start times)	All comparisons	All outcomes	RCT:≤2 per comparison					Sparse	Unclear	Insufficient

This table presents the pairwise results of comparisons for which there was sufficient evidence. It does not include pairwise results for which the evidence was graded "insufficient" strength of evidence [SoE]). Other abbreviations: CI = confidence interval, DVT = deep vein thrombosis, NMA = network meta-analysis, OR = odds ratio, RCT = randomized controlled trial.

* Evaluated outcomes included total venothromboembolism (VTE), symptomatic VTE, total pulmonary embolism (PE), fatal PE, symptomatic PE, total deep vein thrombosis (DVT), symptomatic DVT, proximal DVT, postthrombotic syndrome, pulmonary hypertension, major bleeding (total), surgical site or wound bleeding, other major bleeding (specific), surgical site or wound infection, surgical site or wound complications (other than bleeding or infection), heparin-induced thrombocytopenia, mechanical device complications, inferior vena cava filter complications, and other clinically significant adverse events. For each comparison, omitted outcomes had insufficient data with two or fewer studies.

† "Unclear" should be interpreted as no evidence of a difference (in contrast to evidence of no difference).

‡ A third highly imprecise trial had an odds ratio of 0.55 (95% CI 0.05, 5.58)

§ <80% of studies of drug comparison reported given outcome, unless only one missing study (data on all VTE and major bleeding outcomes should have been available in almost all trials; therefore, outcomes were excluded selectively suggesting high risk of bias of reporting bias).

|| Antiplatelet drug, direct thrombin inhibitors, factor VIII inhibitors, factor Xa inhibitors, low molecular weight heparin, mechanical devices, unfractionated heparin, vitamin K antagonist, and combination low molecular weight heparin and mechanical device.

Apixaban, aspirin, dabigatran, dalteparin, darexaban, desirudin, edoxaban, enoxaparin, fondaparinux, heparin (unfractionated), intermittent pneumatic compression device, semuloparin, tinzaparin, venous foot pump, warfarin, combination enoxaparin and graduated compression stocking, and combination enoxaparin and intermittent pneumatic compression.

Discussion

As reviewed in the 2012 venothromboembolism (VTE) report, there is a high strength of evidence (SoE) from prior research that VTE prophylaxis after major orthopedic surgery reduces the incidence of total DVTs, in comparison to no (or placebo) prophylaxis; although the rarity of postoperative pulmonary embolism (PE) makes difficult a definitive answer to whether thromboprophylaxis is effective to reduce PE or death.[1] Systemic (i.e., nonmechanical) interventions also in general increase the risk of postoperative bleeding, compared to no (or placebo) prophylaxis.[1] Because of the presumed strong relationship between deep vein thrombosis (DVT; particularly proximal DVTs) and resultant PE, some form of thromboprophylaxis has become standard of care after major orthopedic surgery. The question of the relative effectiveness and safety of different thromboprophylaxis interventions remained uncertain as of the 2012 VTE report.

A large volume of evidence has been garnered comparing intervention options to prevent VTE in patients undergoing total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgery. In total this systematic review addressing comparative effectiveness and harms of drug and mechanical interventions included 127 randomized controlled trials (RCTs) and 15 large nonrandomized comparative studies (NRCSs) examining head-to-head comparisons. The review explicitly evaluates direct comparative information and does not examine placebo-controlled effectiveness studies (with the exception of including placebo trials in the network meta-analyses). These studies pertain to three different surgeries and include nine different classes of intervention and 21 specific interventions (plus 6 combinations of classes or interventions). Furthermore, the studies disproportionately (78%) evaluated low molecular weight heparin (LMWH) and enoxaparin in particular (60%). Thromboprophylactic interventions that are most likely to have lower risk of major bleeding (particularly aspirin and mechanical devices, for which there is limited research funding support compared with newer pharmaceutical interventions) have been inadequately studied in direct comparison studies, severely limiting strong conclusions regarding their relative effectiveness and safety. In addition, studies implicitly used a variety of specific orthopedic surgical techniques, but generally failed to describe these sufficiently to allow cross-study comparisons based on surgical techniques (or VTE- or bleeding-risk status of patients); no study reported within-study comparisons of different patients based on these characteristics. Studies also differed in regard to the specific VTE outcomes that were reported. Most studies reported total DVT (82%), which includes asymptomatic DVTs and is thus not routinely diagnosed and may not be clinically important as pertains to PE and other clinical vascular outcomes. Between one-third and two-thirds of studies did not report the other, more clinically important, VTE outcomes (e.g., symptomatic DVT). Based on an imperfect analysis across generally relatively small studies, we found that rates of total DVT are not correlated with rates of total PE ($r=0.07$); although, this analysis is also hampered by the fortuitous fact that few study participants had a PE. Because PEs are relatively rare, total DVTs have become a common primary outcome for VTE prophylaxis studies in part to increase power (since total DVTs are more common than symptomatic DVTs); however, reliance on this outcome may result in biased conclusions if some interventions are more effective at preventing asymptomatic or distal DVTs (and thus total DVTs) but not more effective at preventing clinically significant DVTs. Because of (potentially biased) incomplete reporting of all VTE outcomes, it is not possible to assess whether total DVT is an appropriate proxy for PE, death, or long-term sequelae secondary to DVTs.

The current review summarizes several advances in the literature base and interpretation since the 2012 VTE report. Newer studies led to a clearer understanding that there is a tradeoff between VTE and major bleeding with either LMWH or direct thrombin inhibitors (DTIs). There are also new studies of factor Xa inhibitors (FXaI), but its relative effect compared to LMWH remains unclear due to inconsistencies across different VTE outcomes and adverse events. Observational studies allowed a new conclusion that LMWH and aspirin have similar effects on total PE, symptomatic DVT, and major bleeding, with low SoE. New evidence also supports tradeoffs between higher and lower dose LMWH and DTI in regards to VTE outcomes and major bleeding, and that higher dose FXaI results in lower risk of total VTE than lower dose. Compared to the 2012 VTE report, similar conclusions were reached regarding the relative benefits of LMWH over unfractionated heparin (UFH), the tradeoff between VTE and major bleeding with LMWH versus VKA, and the superiority of longer duration LMWH than shorter duration.

The large majority of studies compared different intervention classes (relevant to Key Question 1), but few compared specific interventions within a class (Key Question 2); different doses, regimens, or intervention durations (Key Question 3); combinations of intervention classes (Key Question 4); or different treatment start times (Key Question 6). Therefore, many of the conclusions (answers to the Key Questions) are highly limited due to insufficient evidence. In particular, conclusions are limited to the specific intervention comparisons and outcomes for which there was sufficient evidence. In addition, for most analyses, there is substantial concern about reporting bias (see *Evidence and Analysis Limitations*).

When summarizing a body of evidence, different approaches can be taken to draw conclusions from the evidence and to determine SoE. The choice of approach can have major impact on determining whether interventions differ in their effects, interventions have similar effects, or data are inconclusive (or insufficient) regarding relative effect. Specific users of the this evidence summary may differ in the assumptions they would make (e.g., whether statistically nonsignificant effects can be said to favor one intervention over another) or in the choice of minimal differences thought to be clinically important. This summary of the evidence uses a threshold of less than 0.80 or greater than 1.20 to suggest that an intervention is favored to reduce the risk of the given outcome, regardless of statistical significance, analogous to a minimal clinical important difference of approximately 20 percent. Notably, statistically nonsignificant effect sizes greater than 20 percent could yield (low SoE) conclusions of differences in effect between interventions.

Evidence Summary

Total Hip Replacement

In summary, from direct comparisons for THR the evidence suggests that

- There is a tradeoff between LMWH and DTI, such that DTI prevents more total DVTs (moderate SoE) and proximal DVTs (moderate SoE) but LMWH results in less major bleeding (low SoE)
- The evidence is inconsistent regarding LMWH and FXaI in that studies reported that FXaI better lowers risk of total VTE (low SoE), total DVT (moderate SoE), and proximal DVT (moderate SoE), but LMWH better lowers the risk of symptomatic VTE (low SoE) and symptomatic DVT (low SoE). There is high SoE that LMWH is better to prevent major bleeding, but both classes have similar rates of study-defined serious adverse

events (moderate SoE). The inconsistencies in these finding suggest important reporting bias.

- Evidence regarding LMWH vs. UFH overall favors LMWH with lower risk of total PE (high SoE), proximal DVT (moderate SoE), and major bleeding (moderate SoE); risk of total DVT is similar between drug classes (moderate SoE).
- The relative effect of LMWH vs. vitamin K antagonists (VKA) is unclear. There is insufficient evidence regarding the relative benefit of either drug class to lower the risk of any VTE outcome, but VKA results in lower risk of major bleeding (high SoE).
- LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding (all low SoE, based on observational studies).
- The relative effect of VKA vs. mechanical devices is unclear. VKA results in lower risk of proximal DVT (high SoE), but insufficient evidence all favors mechanical devices to lower the risk of total DVT, and adverse events data have not been reported.
- The relative effect of lower vs. higher dose FXaI is unclear. Higher dose FXaI has a lower risk of total VTE (low SoE), but there is insufficient evidence for other outcomes, including adverse events.
- There is a tradeoff between lower and higher dose LMWH, such that higher dose LMWH has a lower risk of total DVT (low SoE), both dose levels have similar risks of proximal DVT (moderate SoE), and lower dose LMWH has a lower risk of major bleeding (moderate SoE).
- The evidence favors longer duration LMWH (>2 weeks) over shorter duration LMWH (up to 10 days or to hospital discharge), with lower risk of total PE (low SoE), total DVT (high SoE), and proximal DVT (moderate SoE) and rare occurrences of major bleeding with any duration.

Network meta-analyses pertain only to total DVT and major bleeding; they suggest that

- FXaI and DTI may be most effective to prevent total DVT compared with mechanical devices, LMWH, VKA, and UFH (moderate SoE)
- LMWH is more likely to result in fewer major bleeding events than FXaI (low SoE)
- Dalteparin is most likely to be most effective to prevent total DVTs compared with enoxaparin, intermittent pneumatic compression devices, UFH, and warfarin (moderate SoE)

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis was inconclusive regarding differential risks of bleeding with LMWH and DTI by chronic kidney disease category. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Total Knee Replacement

Fewer studies of TKR (than THR) yielded fewer conclusions with sufficient evidence. In summary, from direct comparisons for TKR the evidence
suggests that

- The relative effect of FXaI vs. LMWH is unclear. FXaI results in a lower risk of total VTE (low SoE), total DVT (low SoE), and proximal DVT (moderate SoE), but similar

risks for symptomatic DVT (low SoE); risk of major bleeding is lower with LMWH (low SoE) but risk of study-defined serious adverse events is lower with FXaI (low SoE).
- There is a tradeoff between LMWH and VKA, such that LMWH better lowers risk of total DVT (high SoE) and proximal DVT (low SoE), but VKA has a lower risk of major bleeding (low SoE).
- There is a tradeoff between lower and higher dose DTI, such that higher dose DTI (dabigatran 220 to 225 mg) has a lower risk of total DVT (high SoE) and proximal DVT (moderate SoE) than lower dose (dabigatran 150 mg), but lower dose DTI has less risk of major bleeding (low SoE).
- The relative effect of lower vs. higher dose FXaI is unclear. Higher dose FXaI results in a lower risk of total VTE (moderate SoE), symptomatic DVT (low SoE), and proximal DVT (low SoE); however, there is insufficient evidence for adverse events.

From network meta-analyses,

- FXaI is more likely to be effective to prevent total DVT than LMWH (low SoE)

Most outcomes were not reported by many studies, resulting in a high risk of reporting bias across the evidence base. A within-study subgroup analysis did not find a substantial difference in relative effect of antiplatelet drug versus mechanical device between unilateral or bilateral TKR surgery. Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Hip Fracture Surgery

Only 12 eligible studies evaluated thromboprophylaxis interventions in patients who underwent HFx surgery. Most specific comparisons were addressed by only one study.

- The relative effect of LMWH and FXaI is unclear. LMWH results in lower risk of total DVT than FXaI (moderate SoE), but there is insufficient evidence for other outcomes.
- For all other comparisons and for all other Key Questions the SoE is insufficient regarding HFx surgery.

Evidence and Analysis Limitations

As noted in the evidence summary, despite the large number of trials addressing thromboprophylaxis in patients undergoing major orthopedic surgery, there is inadequate evidence to confidently compare the effectiveness and the major adverse events of the myriad treatment options. As noted, the large majority of evidence pertains to LMWH (specifically enoxaparin), limiting the ability to compare all interventions. In particular, there are sparse RCTs or NRCSs that evaluated antiplatelet drugs (e.g., aspirin), VKA (e.g., warfarin), or mechanical devices. However, the network meta-analyses are subject to important caveats. The sparseness of direct comparisons between most interventions within each network weakened the structure and the conclusions from the network meta-analyses. The only VTE outcome with sufficient evidence to allow network meta-analysis was total DVT, which is of questionable clinical significance since it includes asymptomatic and distal DVTs which have not been demonstrated to be associated with increased risk of PE. It is also important to recognize that the ranking of interventions by network meta-analysis may not be stable and may be susceptible to change with the addition of more studies; the ranking orders are also not supported by evaluations of statistical significance. However, network meta-analysis findings were consistent with direct, pairwise comparisons of interventions to lower the risk of total DVT and major bleeding.

The network meta-analyses provided greater power to compare all intervention classes and all interventions, but the sparseness of direct (within-study) comparisons for many of the interventions meant that meaningful conclusions could be derived for only a small subset of the interventions.

Further hampering evaluation of the trials, studies were not consistent in which specific outcomes were reported. Notably only total DVT was reported by more than 80 percent of the studies. However, as discussed, this outcome is of unclear clinical importance. Only about half of studies reported major bleeding, the adverse event of greatest concern for most interventions. Most of the VTE outcomes were reported by 50 percent or fewer of the studies. Only one study reported all VTE and adverse event outcomes of primary interest to our panel of stakeholders and only two studies reported all VTE outcomes. Full reporting of VTE outcomes and adverse events by trials would have allowed greater SoE for almost all intervention classes and several specific interventions. However, studies arbitrarily or selectively reported specific outcomes.

Our analyses did not find significant evidence of bias due to industry funding, based on subgroup meta-analysis comparisons of industry-funded vs. other studies. However, 54 percent of the trials were industry-supported and only 13 percent of RCTs explicitly reported no industry support, which might partially explain the selective outcome reporting.[167, 168] The relatively small number of RCTs available for meta-analysis for any given comparison and the small percentage of studies explicitly with no industry support meant that our analyses of industry funded required us to combine RCTs with no industry support and those that did not report funding source. If many of the studies that did not report funding were in fact industry-funded, then any real funding-source bias would have been diluted by the misclassification of funding source. Under the assumption that industry is most likely to fund and publish studies designed to be favorable to their products, the fact that the majority of evidence is industry-supported may explain the selective outcome reporting across studies (if favorable outcomes were more likely to be reported and nonfavorable outcomes omitted), the preponderance of evidence regarding enoxaparin, the sparseness of evidence on aspirin and mechanical devices, and relative sparseness of head-to-head trials of newer drugs (as opposed to comparisons with UFH or placebo).

The RCTs were generally consistent in regard to their eligibility criteria, mostly including all-comers without contraindications. This approach improves the applicability of the individual trials (and thus of the systematic review). Nonetheless, effect sizes in subgroups were rarely reported in these RCTs, and it greatly hampered our ability to evaluate potential explanations for heterogeneity or to hypothesize about possible subgroup differences based on patient history or surgery or anesthesia characteristics. Other than funding source, we were able only to evaluate potential differences between Asian and non-Asian studies. Overall, we found no significant difference between studies conducted in different regions (among analyzable studies), except major bleeding for the comparison of LMWH and FXaI in patients undergoing THR (summary OR in Asian RCTs 1.95, 95% CI 0.46 to 8.22; summary OR in non-Asian studies 0.68, 95% CI 0.49 to 0.94). Nevertheless, the event rates in the Asian studies were generally lower than the non-Asian studies. It suggests incomparability in the two populations besides ethnicity, which might explain the potential difference in the treatment effects. Only two RCTs reported on within-study subgroup analyses based on chronic kidney disease category (major bleeding, enoxaparin vs. desirudin) and by unilateral versus bilateral TKR surgery (DVT, aspirin vs. compression boots). Neither study found a significant difference in treatment effect in the different subgroups. Differences in effectiveness and safety between numerous different

subgroups could not be evaluated due to lack of reporting of such analyses, including by age, sex, race, thrombosis risk factors, bleeding risk factors, comorbidities, medication use, or surgery types or techniques.

Of note, this review evaluated the evidence as per the *a priori* protocol, which was built off of, and relied on, the 2012 VTE report.[13] Acknowledging that evidence for some interventions (e.g., mechanical devices) was likely to be sparse, we included larger NRCS. However, the smaller NRCSs that were excluded may have provided additional evidence, particularly for mechanical devices. While we did not reevaluate (mostly old) placebo-controlled RCTs among the direct comparisons between interventions, these studies were included in the NMAs. This review also did not cover numerous pertinent clinically important questions including comparisons of different strategies (e.g., aspirin and mechanical devices for low-risk patients and LMWH for high-risk patients). There are multiple standard methods for accounting for evidence in three (or more) arm studies in meta-analyses, when two (or more) of the arms are the same intervention (e.g., at different doses). In these instances, we chose the simplest method, which may be most clinically relevant in that we chose to analyze only the U.S. Food and Drug Administration (FDA)-approved dose. When this was not possible, we selected the arm with the largest sample size (among FDA-approved or commonly used doses).

Future Research Recommendations

Much of the evidence base is insufficient to allow confident conclusions. Much of this lack is due to a relative sparseness of evidence evaluating interventions other than LMWH, and enoxaparin in particular. A more complete evidence base for the other treatments would allow for a stronger ranking of intervention classes, and of specific interventions, in term of risk of VTE and risk of major bleeding (and other adverse events). Currently, there has been substantially more research conducted in patients undergoing THR than TKR; further studies regarding TKR may be warranted. In particular, few RCTs have been conducted in HFx surgery.

To avoid real and perceived bias (including, in particular concerns about reporting bias), ideally, a greater number of studies should be funded independently of industry. Furthermore, to minimize bias, all studies should report the full range of outcomes of interest, regardless of study results. Trial registration *in priori* and standard reporting compliant with the Consolidated Standards of Reporting Trials (CONSORT) statement also help reduce potential reporting bias. For VTE prophylaxis studies, there is a fairly standard list of VTE and adverse event outcomes that are generally accepted as being of interest. This systematic review covers a complete list of outcomes that should be reported by all studies. To reduce the risk of bias in systematic reviews, all outcomes, particularly symptomatic DVT and PE and including those with no events, should be reported. However, to improve applicability of future studies to real-world clinical practice (where radiographic searches for asymptomatic DVTs are not performed), we would recommend that RCT protocols *not* mandate postsurgical diagnostic testing for asymptomatic DVTs.

This review made no assumptions about unreported event rates. Therefore, since mechanical device studies rarely reported bleeding (or other adverse event) outcomes, our pairwise and network meta-analysis review of mechanical devices had insufficient evidence about risk of bleeding. Ideally, all existing RCTs should report their full set of outcome results. This can relatively easily be done by submitting trial results to a publicly-accessible registry such as ClinicalTrials.gov.

Larger RCTs should evaluate differences in treatment and adverse event effects in relevant subgroups of patients. Ideally, these analyses should be adequately powered. Based on our

discussions with a panel of clinical experts and other key informants, the following subgroup analyses are of interest: sex, race/ethnicity, age, body weight, tobacco use, chronic disease, varicosities, history of bleeding disorders or surgical bleeding, prior VTE, presurgical use of antiplatelet drugs or warfarin, or hormones, unilateral versus bilateral surgery, use of cemented fixation, tourniquet use, tranexamic acid use, and anesthesia type. A small number of trials were explicitly limited to some of these subgroups (including no presurgical use of antithrombotics and unilateral surgery), the counterfactuals (e.g., only presurgical antithrombotics or bilateral surgery) have not been studied. Since it is unlikely that RCTs will focus on these rarer and higher-risk factors, it is more important for researchers to evaluate the subgroups within their studies, when available.

Conclusions and Clinical Implications

While a large body of RCT evidence exists on comparative effectiveness and harms of thromboprophylaxis interventions after major orthopedic surgery, none of the Key Questions are fully and adequately addressed. For most Key Questions, the evidence base was too sparse to allow conclusions with sufficient SoE. For the comparisons of different interventions classes, only selective pairs of intervention classes had sufficient evidence, but often only for selective outcomes. The largest body of evidence exists for THR, with fewer studies of TKR, and very few studies of HFx surgery. The large majority of head-to-head studies evaluated LMWH (enoxaparin, in particular) with relatively few studies evaluating other intervention classes. Only a small minority of studies reported no industry support. Studies did not regularly report on all VTE-related and adverse effect outcomes, resulting in important possible reporting bias. Studies mostly reported total DVT, an outcome with unclear clinical significance. Almost no studies reported subgroup analyses. These limitations restrict the conclusions that can be drawn from the body of evidence.

Based on head-to-head comparisons for which there is sufficient evidence to make conclusions, LMWH is more effective to prevent VTE outcomes (with moderate to high SoE) and safer to prevent major bleeding (moderate SoE) than UFH (in patients undergoing THR). There are tradeoffs between LMWH and DTI (for THR) such that DTI is more effective to prevent total and proximal DVTs (moderate SoE), but LMWH results in less major bleeding (low SoE). Similarly there are tradeoffs between LMWH and VKA (for TKR) such that LMWH is more effective to prevent proximal and total DVTs (low and high SoE, respectively), but VKA results in less major bleeding (low SoE). Based primarily on a very large, well conducted observational study (with propensity score analyses), there is low SoE that LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding after THR. Comparisons between LMWH and FXaI, and between other pairs of treatment classes, are inconclusive due to either conflicting evidence across specific types of VTE or different adverse events or because of insufficient direct comparative evidence.

Two other findings of note are that for both LMWH (in THR) and DTI (in TKR) there is variable SoE that higher dose LMWH or DTI is more effective to prevent DVT but lower doses result in less major bleeding. Evidence is insufficient regarding different doses of other drug classes, different durations of treatment, comparisons of specific interventions, evaluations of combinations of interventions, and comparisons of timing of when to start thromboprophylaxis.

Of particular note, the inconsistent evidence LMWH versus FXaI was very likely due to selective outcome reporting. As an example, for THR, among 11 RCTs, only 6 reported on total VTE (favoring FXaI) and only 7 reported on symptomatic VTE (favoring LMWH), of which

only 3 trials reported both outcomes. Selective outcome reporting was a major concern across all the analyses and in this case may have resulted in inconsistent conclusions across outcomes.

Due to a lack of sufficient direct comparisons between interventions for most outcomes of interest, we were able to construct network meta-analyses (to simultaneously evaluate both direct and indirect comparisons among all interventions) only for total DVT and major bleeding. For these outcomes network meta-analysis found that, for THR there is moderate SoE that FXaI is most effective to prevent total DVT; LMWH has lower risk of major bleeding that FXaI (low SoE). For TKR, by network meta-analysis we can conclude only that there is low SoE that FXaI is more effective to prevent total DVT than LMWH; there is insufficient evidence regarding major bleeding. Data are too sparse for HFx surgery to make conclusions from network meta-analysis. These analyses pertain to total DVT and major bleeding only.

In the face of incomplete and unclear evidence, patient and clinician preferences and values regarding the relative importance of avoiding VTE (primarily DVT) and major bleeding (and subsequent sequelae). While clinicians, policymakers, and clinical practice guideline developers should consider this evidence regarding relative effectiveness and safety of different thromboprophylaxis regimens (and its deficiencies), it may be reasonable to also consider other sources of evidence not covered here (e.g., other observational research and assumptions related to mechanisms of action) to aid with decisionmaking in the face of incomplete evidence.

Future studies, particularly of interventions other than enoxaparin, are needed to address most Key Questions. These studies, and if feasible existing studies, should report all VTE-related and adverse event outcomes. Larger trials should conduct and report subgroup analyses of interest. Ideally, more future studies should be funded independently of industry to avoid real and perceived bias.

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Appendix A. Search Strategy

PubMed Search

("Arthroplasty, Replacement, Knee"[Mesh] or ("Arthroplasty"[Mesh] and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or "Knee Prosthesis"[Mesh] or knee prosthesis or knee joint or "Arthroplasty, Replacement, Hip"[Mesh] or total hip replacement or hip arthroplasty or thr or "Hip Prosthesis"[Mesh] or Hip Prosthesis or hip fracture surgery or hfs or (("Fracture Fixation, Internal"[Mesh] or "Fracture Fixation, Intramedullary"[Mesh]) and (hip femur or femor* or tibia* or ankle or foot)) or (arthroscop* and (knee or meniscectomy or synovectomy or cruciate ligament)) or "Casts, Surgical"[Mesh] or surgical cast or plaster cast or splint* or "Splints"[Mesh] or Achilles tendon or tibial plateau fracture or distal femur fracture or (lumbar and (laminectomy or discectomy or fusion)) or (osteotomy AND (femur OR femor* OR tibia*)))

AND

("Pulmonary Embolism"[Mesh] or pulmonary embol* or pulmonary thromboembol* or PE or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or "Venous Thromboembolism"[Mesh] or venous thromboembol* or VTE or "Venous Thrombosis"[Mesh] or venous thrombos* or clot)

AND

("Anticoagulants"[Mesh] OR "Aspirin"[Mesh] or aspirin or clopidogrel or ticlopidine or prasugrel or "Heparin"[Mesh] or "Heparinoids"[Mesh] or heparin or UFH 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 apixaban or enoxaparin or "Hirudins"[Mesh] or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or "Warfarin"[Mesh] or warfarin or "4-Hydroxycoumarins"[Mesh] or acenocoumarol or dicoumarol or "Dextran Sulfate"[Mesh] or dextran sulfate or "Stockings, Compression"[Mesh] or ((compression or elastic) and (stocking* or boot*)) or GCS or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices"[Mesh] or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or "Vena Cava Filters"[Mesh] or vena cava filter* or IVC or "Factor Xa Inhibitors"[Mesh])

AND

("Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study" [Publication Type] OR ((comparative or Intervention) AND study) OR "Intervention Studies"[Mesh] OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR “before and after” OR interrupted time* OR time serie* OR intervention* OR (("quasi-experiment*" OR

quasiexperiment* OR quasi or experimental) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR "Clinical Studies" [Publication Type] OR "Clinical Studies as Topic"[Mesh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct)

Limit 2010-

Cochrane

((Arthroplasty and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or "Knee Prosthesis"[Mesh] or knee prosthesis or knee joint or total hip replacement or hip arthroplasty or thr or Hip Prosthesis or hip fracture surgery or hfs or ((Fracture Fixation Internal or Fracture Fixation Intramedullary) and (hip femur or femor* or tibia* or ankle or foot)) or (arthroscop* and (knee or meniscectomy or synovectomy or cruciate ligament)) or surgical cast or plaster cast or splint* or Achilles tendon or tibial plateau fracture or distal femur fracture or (lumbar and (laminectomy or discectomy or fusion)) or (osteotomy AND (femur OR femor* OR tibia*)))
AND
(Pulmonary Embolism or pulmonary embol* or pulmonary thromboembol* or PE or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or Venous Thromboembolism or venous thromboembol* or VTE or Venous Thrombosis or venous thrombos* or clot)
AND
(Anticoagulants or Aspirin or clopidogrel or ticlopidine or prasugrel or Heparin or Heparinoids or UFH 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 apixaban or enoxaparin or Hirudins or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or Warfarin or warfarin or 4-Hydroxycoumarins or acenocoumarol or dicoumarol or (dextran and sulfate) or ((compression or elastic) and (stocking* or boot*)) or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices" or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or vena cava filter* or IVC or Factor Xa Inhibitors)

Limit 2010-

Embase

((Arthroplasty and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or knee prosthesis or knee joint or total hip replacement or hip arthroplasty or Hip Prosthesis or hip fracture surgery or (Fracture Fixation and (femur or femor*)))
AND
(Pulmonary Embolism or pulmonary embol* or pulmonary thromboembol* or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or Venous Thromboembolism or venous thromboembol* or VTE or Venous Thrombosis or venous thrombos* or clot)

AND
(Anticoagulants or Aspirin or clopidogrel or ticlopidine or prasugrel or Heparin or Heparinoids or UFH 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 apixaban or enoxaparin or Hirudins or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or Warfarin or warfarin or 4-Hydroxycoumarins or acenocoumarol or dicoumarol or (dextran and sulfate) or ((compression or elastic) and (stocking* or boot*)) or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices" or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or vena cava filter* or IVC or Factor Xa Inhibitors)
AND
(cohort OR (follow-up or followup) OR longitudinal OR placebo* OR ((comparative or Intervention) AND study) OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR (before and after) OR interrupted time* OR time serie* OR intervention* OR ((quasi-experiment* OR quasiexperiment* OR quasi or experimental) and (method or study or trial or design*)) OR (case and control) OR clinical stud* OR clinical trial OR random allocation OR double-blind method OR single-blind method OR random* OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct)
AND
Limit 2010-

Surveillance Search

For this surveillance document, we searched PubMed on July 16, 2015, using the following strategy:

("Arthroplasty, Replacement, Knee"[Mesh] or ("Arthroplasty"[Mesh] and (knee or hip)) or total knee replacement or knee arthroplasty or tkr or "Knee Prosthesis"[Mesh] or knee prosthesis or knee joint or "Arthroplasty, Replacement, Hip"[Mesh] or total hip replacement or hip arthroplasty or thr or "Hip Prosthesis"[Mesh] or Hip Prosthesis or hip fracture surgery or hfs or (("Fracture Fixation, Internal"[Mesh] or "Fracture Fixation, Intramedullary"[Mesh]) and (hip femur or femor* or tibia* or ankle or foot)) or (arthroscop* and (knee or meniscectomy or synovectomy or cruciate ligament)) or "Casts, Surgical"[Mesh] or surgical cast or plaster cast or splint* or "Splints"[Mesh] or Achilles tendon or tibial plateau fracture or distal femur fracture or (lumbar and (laminectomy or discectomy or fusion)) or (osteotomy AND (femur OR femor* OR tibia*)))

AND

("Pulmonary Embolism"[Mesh] or pulmonary embol* or pulmonary thromboembol* or PE or deep vein thrombos* or deep venous thrombos* or deep venous thromboembol* or deep vein thromboembol* or DVT or "Venous Thromboembolism"[Mesh] or venous thromboembol* or VTE or "Venous Thrombosis"[Mesh] or venous thrombos* or clot)

AND

("Anticoagulants"[Mesh] OR "Aspirin"[Mesh] or aspirin or clopidogrel or ticlopidine or prasugrel or "Heparin"[Mesh] or "Heparinoids"[Mesh] or heparin or UFH 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 "Hirudins"[Mesh] or desirudin or argatroban or bivalirudin or lepirudin or dabigatran or "Warfarin"[Mesh] or warfarin or "4-Hydroxycoumarins"[Mesh] or acenocoumarol or dicoumarol or "Dextran Sulfate"[Mesh] or dextran sulfate or "Stockings, Compression"[Mesh] or ((compression or elastic) and (stocking* or boot*)) or ~~GCS~~ or venous foot pump or VFP or "Intermittent Pneumatic Compression Devices"[Mesh] or pneumatic compression or pneumatic hose or pneumatic compression hose or IPC or "Vena Cava Filters"[Mesh] or vena cava filter* or IVC or "Factor Xa Inhibitors"[Mesh])

AND

((randomized controlled trial [pt] or controlled clinical trial [pt] or random* or placebo or trial or groups or blind) not (animals not humans))

Appendix B. Excluded Studies

Table B1. Excluded studies

PubMed ID	Authors	Title	Journal	Rejection Reason
7706340	Abdel-Salam A, Eyres K{Abdel-Salam, 1995 #111}	Effects of tourniquet during total knee arthroplasty: A prospective 1andomized study	J Bone Joint Surg 1995;77-B:250-3	No intervention of interest
24026260	Adam SS and McDuffie JR and Lachiewicz PF and Ortel TL and Williams JW Jr{Adam, 2013 #28}	Comparative effectiveness of new oral anticoagulants and standard thromboprophylaxis in patients having total hip or knee replacement: a systematic review.		Duplicate publication (no additional data)
23808982	Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI {Agnelli, 2013 #120}	Oral apixaban for the treatment of acute venous thromboembolism	N Engl J Med 2013;369:799e808	Not population of interest
18485453	Agnelli G, Eriksson BI, Cohen AT, Bergqvist D, Dahl OE, Lassen MR, Mouret P, Rosencher N, Andersson M, Bylock A, Jensen E, Boberg B {Agnelli, 2009 #121}	Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran	Thromb Res 2009; 123: 488–97	Pre-2010 (presumably excluded by Uconn)
17408408	Agnelli G, et al {Agnelli, 2007 #122}	A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement	J Thromb Haemost 5 (4) (2007) 746–753	Pre-2010 (presumably excluded by Uconn)
23857692	Akpinar EE and Hosgun D and Akan B and Ates C and Gulhan M {Akpinar, 2013 #31}	Does thromboprophylaxis prevent venous thromboembolism after major orthopedic surgery?		No comparison of interest
EMBASE 70613300	Anderson D R; Dunbar M; Venitolli P A; Kahn S; Belzile E; Bohm E; Fisher W; Gross P; Kim P; Gofton W; MacDonald S; Pelet S; Crowther M; Pleasance S; Rodger M; Wells P; Kovacs M; Andreou P {Anderson, 2011 #123}	A randomized controlled trial comparing aspirin with dalteparin for the prevention of venous thromboembolism following total hip arthroplasty (2011)	Journal of thrombosis and haemostasis : JTH, 2011, 9, 303	Duplicate publication (no additional data)
NCT01720108	Anderson DR	Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty (EPCAT II) (2012)	https://clinicaltrials.gov/ct2/show/NCT01720108	No results reported
23732713	Anderson DR1, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, Fisher W, Gofton W, Gross P, Pelet S, Crowther M,	Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial	Ann Intern Med. 2013 Jun 4;158(11):800-6	Not primary study

PubMed ID	Authors	Title	Journal	Rejection Reason
	MacDonald S, Kim P, Pleasance S, Davis N, Andreou P, Wells P, Kovacs M, Rodger MA, Ramsay T, Carrier M, Vendittoli PA. {Anderson, 2013 #35}			
24384784	Argun M and Oner M and Saglamoglu M and Karaman I and Guney A and Halici M and Halil Kafadar I {Argun, 2013 #21}	Fondaparinux versus nadroparin for prevention of venous thromboembolism after elective hip and knee arthroplasty.		Combined TKR and THR
noPMID 10	Arti H; Rouzbahani R {Arti, 2013 #124}	Comparing the effectiveness results of heparin and enoxaparin after total hip artroplasty. [Persian] (2013)	Journal of Isfahan Medical School;Jun2013, Vol. 31 Issue 231, p381	nRCS N<750
21053884	Asensio A; Antolin F J; Sanchez-Garcia J M; Hidalgo O; Hernandez-Navarrete M J; Bishopberger C; Miguel L G; Gay-Pobes A; Cabrera-Quintero A; Asensio {Asensio, 2010 #81}	Timing of DVT prophylaxis and risk of postoperative knee prosthesis infection (2010)	Orthopedics	nRCS N<750
CN-00441869	Barden B, Kröger K, Löer F {Barden, 2001 #125}	Intraoperative Dopplersonography of the femoral vein for maintenance of venous flow in a hip endoprosthesis	Unfallchirurg 2001;104:138-42	No intervention of interest
23989471	Barg {Barg, 2013 #30}	[Thromboembolic complications following ankle prosthesis implantation]		Not surgery of interest
24078351	Barg {Barg, 2013 #27}	Thrombembolic complications after total ankle replacement		Not surgery of interest
	Barnes RW, Brand RA, Clarke W, Hartley N, Hoak JC {Barnes, 1978 #126}	Efficacy of graded-compression antiembolism stockings in patients undergoing total hip arthroplasty	Clinical Orthopaedics and Related Research 1978;132:61–7	Pre-2010 (presumably excluded by Uconn)
25126354	Baser O and Supina D and Sengupta N and Wang L {Baser, 2011 #73}	Anticoagulation Bridging Therapy Patterns in Patients Undergoing Total Hip or Total Knee Replacement in a US Health Plan: Real-World Observations and Implications.		nRCS N<750
noPMID 01	Baser O; Wang L; Supina D; Sengupta N {Sengupta, 2011 #127}	Anticoagulation prophylaxis practice patterns in patients having total hip, total knee replacement in a US health plan (2011)	Formulary	nRCS N<750
26448724	Bern M M; Hazel D; Deeran E; Richmond J R; Ward D M; Spitz D J; Mattingly D A;	Low dose compared to variable dose Warfarin and to Fondaparinux as prophylaxis for	Thromb J	Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
	Bono J V; Berezin R H; Hou L; Miley G B; Bierbaum B E {Bern, 2015 #1}	thromboembolism after elective hip or knee replacement surgery; a randomized, prospective study (2015)		
Abstract P191	Bern M M; Ward D; Miley G; Spitz D; Spigelman Z; Mattingly D; Williams F; Deeran E; Phillips C	Prospective randomized study of thromboembolic disease (TED) prophylaxis after knee or hip replacement: Fixed low dose warfarin vs. variable dose warfarin vs. fondaparinux, each given for 4 weeks (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
23197272	Beyer-Westendorf J and Lutzner J and Donath L and Tittl L and Knoth H and Radke OC and Kuhlisch E and Stange T and Hartmann A and Gunther KP and Weiss N and Werth S {Beyer-Westendorf, 2013 #46}	Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery: findings from the ORTHO-TEP registry.	Thromb Haemost. 2013 Jan;109(1):154-63	Combined TKR and THR
22882706	Beyer-Westendorf J; Lutzner J; Donath L; Radke O C; Kuhlisch E; Hartmann A; Weiss N; Werth S {Beyer-Westendorf, 2012 #50}	Efficacy and safety of rivaroxaban or fondaparinux thromboprophylaxis in major orthopedic surgery: Findings from the ORTHO-TEP registry (2012)	J Thromb Haemost. 2012 Oct;10(10):2045-52	Combined TKR and THR
	Blanchard J, Meuwly JY, Leyvraz PF, et al {Blanchard, 1999 #128}	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	Pre-2010 (presumably excluded by Uconn)
	Bradley JG, Krugener GH, Jager HJ {Bradley, 1993 #129}	The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty	J Arthroplasty 1993;8:57–61	Pre-2010 (presumably excluded by Uconn)
	Bruun-Olsen V, Heiberg KE, Mengshoel AM {Bruun-Olsen, 2009 #130}	Continuous passive motion as an adjunct to active exercises in early rehabilitation following total knee arthroplasty – a randomized controlled trial	Disability and Rehabilitation 2009;31(4):277–83	Pre-2010 (presumably excluded by Uconn)
	Buller H, Deitchman D, Prins M, Segers A {Buller, 2008 #131}	Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis, The Botticelli DVT dose-ranging study	J Thromb Haemost 2008;6:1313e1318	Pre-2010 (presumably excluded by Uconn)
	Cai wei	The Study of the Efficacy and Safety of VTE Prophylaxis with Rivaroxaban Following Total Hip Replacement	2008, doi:CNKI:CDMD:1 2008 087675	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
27075710	Camporese, G., Bernardi, E., Noventa, F., Bosco, M., Monteleone, G., Santoro, L., Bortoluzzi, C., Freguja, S., Nardin, M., Marullo, M., Zanon, G., Mazzola, C., Damiani, G., Maniscalco, P., Imberti, D., Lodigiani, C., Becattini, C., Tonello, C., Agnelli, G. {Camporese, 2016 #250}	Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study	Thromb Haemost	27075710
20540254	Cao J; Wang J; Zhang H; Wang L {Cao, 2010 #85}	[A combination of arteriovenous impulse system and low-molecular-weight heparins calcium for prophylaxis of deep venous thrombosis following total knee arthroplasty] (2010)	Zhongguo xiu fu chong jian wai ke za zhi = Chinese journal of reparative and reconstructive surgery	nRCS N<750
20812009	Cao Y B; Zhang J D; Shen H; Jiang Y Y {Cao, 2010 #82}	Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials (2010)	Eur J Clin Pharmacol	Duplicate publication (no additional data)
	Chan N; Li C; Lau K K; Chan A K C; Chan H H W {Chan, 2012 #132}	A systematic review evaluating the effects of treatment duration on bleeding due to factor-specific oral anticoagulant therapy (2012)	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH	SR or MA without references (conference abstract)
24813323	Chapelle {Chapelle, 2014 #17}	Prevention of venous thromboembolic events with low-molecular-weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials		Not surgery of interest
25724111	Charters MA and Frisch NB and Wessell NM and Dobson C and Les CM and Silverton CD {Charters, 2015 #7}	Rivaroxaban Versus Enoxaparin for Venous Thromboembolism Prophylaxis after Hip and Knee Arthroplasty.		Combined TKR and THR
	Chen B, Zimmerman JR, Soulen L, DeLisa JA {Chen, 2000 #133}	Continuous passive motion after total knee arthroplasty: a prospective study	American Journal of PhysicalMedicine&Rehabililation 2000;79(5):421–6	Pre-2010 (presumably excluded by Uconn)
noPMID 05	Chen J H; Xi Z L; Yuan Z{Chen J, #134}	Comprehensive prevention of deep vein thrombosis after total hip replacement. [Chinese] (2015)	China Tissue Engineering Research 2015 , Vol 19. Issue	Comparator mixed interventions

PubMed ID	Authors	Title	Journal	Rejection Reason
			(17) : 2642-2647	
Abstract H5	Cho S E; Clark N P; Delate T; Witt D M {Cho, 2011 #135}	Low-intensity warfarin thromboprophylaxis after hip replacement surgery (2011)	Journal of Thrombosis and Thrombolysis	No comparison of interest
22387582	Cohen A and Drost P and Marchant N and Mitchell S and Orme M and Rublee D and Simon TA and Sutton A {Cohen, 2012 #59}	The efficacy and safety of pharmacological prophylaxis of venous thromboembolism following elective knee or hip replacement: systematic review and network meta-analysis.		Duplicate publication (no additional data)
70770566	Cohen A; Pieter D; Marchant N; Mitchell S; Orme M; Simon T; Sutton A; Rublee D	The efficacy and safety of pharmacological prophylaxis of VTE following elective knee or hip replacement: Systematic review and network meta-analysis (2011)	Blood. Conference: 53rd Annual Meeting of the American Society of Hematology, ASH	SR or MA without references (conference abstract)
	Cohen AT, Armstrong D, Gazdzik T, Ryge C, Pak R, Mandema J, et al	An adaptive-design dose-ranging study of PD 0348292, a new oral factor Xa inhibitor, for thromboprophylaxis after total knee replacement surgery [Abstract]	Blood 2008;112:361 Abstract 980	Duplicate publication (no additional data)
	Cohen AT, Skinner JA, Warwick D, Brenkel I {Cohen, 2008 #136}	The use of graduated compression stockings in association with fondaparinux in surgery of the hip: A 5andomized5, multinational, 5andomized, open-label, parallel-group comparative study	J Bone Joint Surg Br 2007; 89: 887–892	Pre-2010 (presumably excluded by Uconn)
22441640	Collinge CA and Kelly KC and Little B and Weaver T and Schuster RD {Collinge, 2012 #58}	The effects of clopidogrel (Plavix) and other oral anticoagulants on early hip fracture surgery.		nRCS N<750
20201479	Colwell {Colwell, 2009 #89}	The ACCP guidelines for thromboprophylaxis in total hip and knee arthroplasty.	Orthopedics	No primary data
24500578	Colwell CW Jr and Froimson MI and Anseth SD and Giori NJ and Hamilton WG and Barrack RL and Buehler KC and Mont MA and Padgett DE and Pulido PA and Barnes CL	A mobile compression device for thrombosis prevention in hip and knee arthroplasty.		No comparison of interest
	Colwell CW Jr, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, et al {Colwell, 2003 #137}	Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement: A randomized, doubleblind study	Journal of Thrombosis and Haemostasis 2003;1 (10):2119–30	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
	Colwell CW Jr, Berkowitz SD, Lieberman JR, Comp PC, Ginsberg JS, Paiement G, et al {Colwell, 2005 #138}	Oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of venous thromboembolism after total knee arthroplasty	Journal of Bone and Joint Surgery – American Volume 2005;87(10):2169–77	Pre-2010 (presumably excluded by Uconn)
	Colwell CW Jr, Spiro TE {Colwell Jr, 1995 #139}	Efficacy and safety of enoxaparin to prevent deep vein thrombosis after hip arthroplasty	Clin Orthop Relat Res 1995; 319: 215-22	Pre-2010 (presumably excluded by Uconn)
	Colwell CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al {Colwell, 2003 #140}	Randomized, doubleblind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR): EXULT B	Blood 2003;102(11):Abstract 39	Pre-2010 (presumably excluded by Uconn)
	Colwell CW, Berkowitz SD, Davidson BL, Lotke PA, Ginsberg JS, Lieberman JR, et al	Randomized, doubleblind, comparison of Ximelagatran, an oral direct thrombin iInhibitor, and Enoxaparin to prevent venous thromboembolism (VTE) after total hip arthroplasty (THA)	Blood 2001;98(11):Abstract 2952	Pre-2010 (presumably excluded by Uconn)
	Colwell CW.	EXULT B: More ximelagatran results in VTE prophylaxis after total knee replacement.	Abstract of the Annual Meeting of the American Society of Hematology (http://www.theheart.org/article/231713.do). (accessed 10 May 2006)	Pre-2010 (presumably excluded by Uconn)
22202495	Dager {Dager, 2012 #65}	Warfarin for Venous Thromboembolism Prophylaxis After Elective Hip or Knee Arthroplasty: Exploring the Evidence, Guidelines, and Challenges Remaining	The Annals of Pharmacotherapy	No primary data
20586919	Dahl O E; Quinlan D J; Bergqvist D; Eikelboom J W {Dahl, 2010 #83}	A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty (2010)	J Thromb Haemost	Duplicate publication (no additional data)
	Dahl O, Eriksson B, Agnelli G, Cohen A, Mouret P, Rosencher N, et al	ASA and NSAIDs with Melagatran/ Ximelagatran or Enoxaparin Do NOT Increase Bleeding in Patients Undergoing Joint Replacement Surgery:	Journal of Thrombosis and Haemostasis 2005;3(1):Abstract P	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
		The METHRO III Study	1627	
	Dahl OE, Eriksson BI, Agnelli G, Cohen AT, Mouret P, Rosencher N, et al	Postoperative melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery: Effects of timing of first dose and risk factors for thromboembolism and bleeding complications on efficacy and safety	Clinical Drug Investigation 2005;25(1): 2005;25(1):65–77	Pre-2010 (presumably excluded by Uconn)
	Darnell J B; Kleppinger E L {Darnell, 2011 #141}	Approved uses of dabigatran etexilate as an anticoagulant (2011)	Journal of Pharmacy Technology	No primary data
23300348	Degli Esposti L and Didoni G and Simon T and Buda S and Sangiorgi D and Degli Esposti E {Degli Esposti, 2013 #45}	Analysis of disease patterns and cost of treatments for prevention of deep venous thrombosis after total knee or hip replacement: results from the Practice Analysis of Thromboprophylaxis after Orthopaedic Surgery (PATHOS) study.		No comparison of interest
21593017	Deitelzweig S B; Lin J; Lin G {Deitelzweig, 2011 #76}	Preventing venous thromboembolism following orthopedic surgery in the United States: Impact of special populations on clinical outcomes (2011)	Clinical and Applied Thrombosis/Hemostasis	No comparison of interest
Abstract P201	Deitelzweig S; Lin J; Lin G {Deitelzweig, 2011 #142}	Impact of special populations on thromboprophylaxis and clinical outcomes of patients undergoing knee replacement surgery in the US (2010)	Circulation: Cardiovascular Quality and Outcomes. Conference: Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke	No comparison of interest
	Denis M, Moffet H, Caron F, Ouellet D, Paquet J, Nolet L {Denis, 2006 #143}	Effectiveness of continuous passive motion and conventional physical therapy after total knee arthroplasty: a randomized clinical	Physical Therapy 2006;86(2):174–85	Pre-2010 (presumably excluded by Uconn)
70917349	Dequen P; Kelly S; Abrams K {Dequen, 2012 #144}	Network meta-analysis of pharmacological interventions to prevent venous thromboembolism following elective knee and hip replacement surgery: Why extend the network? (2012)	Value in Health	SR or MA without references (conference abstract)
25174484	Ding G and Li S and Pan Z and Gao C and	[Effects of batroxobin on perioperative blood loss	Zhonghua Liu Xing	No intervention of interest

PubMed ID	Authors	Title	Journal	Rejection Reason
	Ma H {Ding, 2014 #12}	and coagulation in patients with low molecular weight heparin when undergoing the total hip replacement].	Bing Xue Za Zhi. 2014 Jun;35(6):737-40.	
18056497	Dorr LD, Gendelman V, Maheshwari AV, et al {Dorr, 2007 #96}	Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment	J Bone Joint Surg Am 2007;89:2648-57	No comparison of interest
No PMID	Dose-confirmatory bridging study in total hip replacement. Available at: http://www.clinicaltrial.gov/ct2/show/NCT01205932. Accessed March 15, 2015	No results posted	Dose-confirmatory bridging study in total hip replacement. Available at: http://www.clinicaltrial.gov/ct2/show/NCT01205932. Accessed March 15, 2015	No results posted
21272316	Dranitsaris G and Jelincic V and Choe Y {Dranitsaris, 2011 #79}	Meta regression analysis to indirectly compare dalteparin to enoxaparin for the prevention of venous thromboembolic events following total hip replacement.		Duplicate publication (no additional data)
70514609	Dranitsaris G; Jelincic V; Choe Y {Dranitsaris, 2011 #145}	Meta regression analysis to indirectly compare the safety and efficacy of dalteparin to enoxaparin for the prevention of venous thromboembolic events (VTES) in total hip replacement (THR) surgery (2010)	Value in Health	SR or MA without references (conference abstract)
	Eisele R, Kinzl L, Koelsch T {Eisele, 2007 #146}	Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis	J Bone Joint Surg [Am] 2007;89-A:1050– 1056	Pre-2010 (presumably excluded by Uconn)
Abstract P-TH-273	Eriksson B I; Agnelli G; Gallus A S; Lassen M R; Prins M H; Renfurm R W; Turpie A G G {Eriksson, 2011 #147}	Onyx-3, a double-blind comparison of once- or twicedaily dosing with YM150 (30 or 60 mg daily) for preventing venous thromboembolism after elective hip arthroplasty (2011)	Journal of Thrombosis and Haemostasis	Duplicate publication (no additional data)
Abstract OC645	Eriksson B; Dahl O E; Kurth A A; Hantel S; Huo M H; Hermansson K; Schnee J M; Friedman R J {Eriksson, 2011 #148}	Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty: The re-novate II 8andomized trial (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
	Eriksson BI, Agnelli G, Cohen A, Dahl O, Mouret P, Rosencher N, et al {Eriksson,	Significantly lower need for blood transfusions associated with post-operatively initiated	Thrombosis and Haemostasis	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
	2004 #149}	subcutaneous melagatran/oral ximelagatran compared with enoxaparin	2004;92(2): 428–30	
	Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, et al{Eriksson, 2003 #150}	EXPRESS Study Group, The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study	Journal of Thrombosis and Haemostasis 2003;1(12):2490–6	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, et al{Eriksson, 2002 #151}	The oral direct thrombin inhibitor ximelagatran, and its subcutaneous form melagatran, compared with enoxaparin for prophylaxis of venous thromboembolism (VTE) in total hip or total knee replacement: the EXPRESS study	Blood 2002;100(11 pt2):abstract 299	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, et al {Eriksson, 2003 #152}	Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement	Thrombosis and Haemostasis 2003;89(2):288–96	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Kalebo P, et al{Eriksson, 2002 #153}	A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I, Melagatran for THRombin inhibition in Orthopaedic surgery	Thrombosis & Haemostasis 2002;87(2):231–37	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Baur M, Lindbratt S, Bach D, Ekman S, Close P	Recombinant hirudin, CGP 39393, (TMREVASC), is more effective than enoxaparin as prophylaxis of thromboembolic complications in patients undergoing total hip replacement [Abstract]	Journal of Bone and Joint Surgery British 1997;79-B(Suppl 1):95–6	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, BaurM, Ekman S, Lindbratt S, Bach D, Kalebo P, et al {Eriksson, 1997 #154}	Recombinant hirudin, desirudin (TMREVASC), is more effective than enoxaparin as prophylaxis of thromboembolic complications in patients undergoing total hip replacement	Thrombosis and Haemostasis 1997;564 (Supplement June):Abstract No PD-2309	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, et al{Eriksson, 2002 #155}	Melagatran for Thrombin, inhibition in Orthopaedic Surgery, Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after	Lancet 2002;360(9344): 1441–47	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
		total hip or knee replacement: the METHRO II 10andomized trial		
	Eriksson BI, Borris LC, Friedman RJ, et al {Eriksson, 2008 #156}	Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty	N Engl J Med 2008; 358(26):2765-2775	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Dahl OE, Ahnfelt L, Kälebo P, Stangier J, Nehmiz G, et al {Eriksson, 2004 #157}	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	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Dahl OE, van Dijk CN, Frostick SP, Kurth AA, Rosencher N, et al {Eriksson, 2006 #158}	A new oral aniticoagulant, dabigatran etexilate, is effective and safe in preventing venous thromboembolism after total knee replacement surgery (The RE-MODEL Trial)	Blood 2006;108:173	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, et al {Eriksson, 2007 #159}	A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery	J Thromb Haemost 5 (8) (2007) 1660–1665	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, et al {Eriksson, 2006 #160}	A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement	Circulation 114 (22) (2006) 2374–2381	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, et al {Eriksson, 2007 #161}	Dose-escalation study of rivaroxaban (BAY 59-7939) – an oral, direct Factor Xa inhibitor – for the prevention of venous thromboembolismin patients undergoing total hip replacement	Thromb Res 120 (5) (2007) 685–693	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, et al {Eriksson, 2006 #162}	Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement	J Thromb Haemost 4 (1) (2006) 121–128	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Lindbratt S, Kalebo P{Eriksson, 2000 #163}	Methro II: dose-response study of the novel oral, direct thrombin 10andomize, H 376/ 95 and its subcutaneous formulation melagatran, compared with dalteparin as thromboembolic prophylaxis after total hip knee replacement	Haemostasis 2000;30(Suppl 1):20–1	Pre-2010 (presumably excluded by Uconn)
	Eriksson BI, Wille-Jorgensen P, Kalebo P, et al {Eriksson, 1997 #164}	A comparison of recombinant hirudin with a low-molecularweight heparin to prevent thromboembolic complications after total hip replacement	Journal of Vascular and Interventional Radiology 1998;9(3):530	Duplicate publication (no additional data)

PubMed ID	Authors	Title	Journal	Rejection Reason
22315265	Falck-Ytter Y and Francis CW and Johanson NA and Curley C and Dahl OE and Schulman S and Ortel TL and Pauker SG and Colwell CW Jr {Falck-Ytter, 2012 #60}	Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.		Duplicate publication (no additional data)
15950853	Farag E, Dilger J, Brooks P, et al {Farag, 2005 #99}	Epidural analgesia improves early rehabilitation after total knee replacement	J Clin Anesth 2005;17:281-5	No intervention of interest
Abstract OC681	Fisher W; Agnelli G; George D; Kakkar A k; Lassen M r; Mismetti P; Mouret P; Bregeault M F; Turpie A G G {Fisher, 2009 #165}	Extended venous thromboembolism (VTE) prophylaxis after hip fracture surgery with the ultra-low-molecular-weight heparin (ULMWH) semuloparin (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
Abstract P330	Fisher W; Agnelli G; George D; Kakkar A; Lassen M R; Mismetti P; Mouret P; Destree D; Turpie A G G	The ultra-low-molecular-weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) after hip fracture surgery (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
	Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al {Francis, 2003 #166}	EXULT A Study Group, Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement	New England Journal of Medicine 2003;349 (18):1703–12	Pre-2010 (presumably excluded by Uconn)
	Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al	Randomized, doubleblind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR)	Journal of Thrombosis and Haemostasis 2003;1(Suppl 1):Abstract P1912	Pre-2010 (presumably excluded by Uconn)
	Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement GD, et al {Francis, 2002 #167}	Randomized, doubleblind, comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR)	Blood 2002;100 (11 pt 2):Abstract 300	Pre-2010 (presumably excluded by Uconn)
	Francis CW, Davidson BL, Berkowitz SD, Lotke PA, Ginsberg JS, Lieberman JR, et al {Francis, 2001 #168}	Randomized doubleblind, comparative study of ximelagatran (pINN, formerly H 376/95), an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee arthroplasty (TKA)	Thrombosis and Haemostasis 2001;July Suppl:Abstract OC44	Pre-2010 (presumably excluded by Uconn)
	Francis CW, Davidson BL, Berkowitz SD,	Ximelagatran versus warfarin for the prevention	Annals of Internal	Pre-2010 (presumably

PubMed ID	Authors	Title	Journal	Rejection Reason
	Lotke PA, Ginsberg JS, Lieberman JR, et al {Francis, 2002 #169}	of venous thromboembolism after total knee arthroplasty, A randomized, double-blind trial	Medicine 2002;137(8):648–55	excluded by Uconn)
	Fredin H, Bergqvist D, Cederholm C, Lindblad B, Nyman U {Fredin, 1989 #170}	Thromboprophylaxis in hip arthroplasty, Dextran with graded compression or preoperative dextran compared in 150 patients	Acta Orthopaedica Scandinavica 1989;60(6): 678–81	Pre-2010 (presumably excluded by Uconn)
18534456	Froimson MI, Murray TG, Fazekas AF {Froimson, 2009 #94}	Venous thromboembolic disease reduction with a portable pneumatic compression device	J Arthroplasty 2009;24:310-6	Combined TKR and THR
	Fuji T, Fujita S, Ochi T {Fuji, 2008 #171}	Fondaparinux prevents venous thromboembolism after joint replacement surgery in Japanese patients	Int Orthop 2008;32(4):443-451	Pre-2010 (presumably excluded by Uconn)
	Fuji T, Wang C, Fujita S, Tachibana S, Kawai Y, Koretsune Y, et al {Fuji, 2010 #172}	Edoxaban versus enoxaparin for thromboprophylaxis after total knee replacement: the STARS E-3 trial	Presented at 21st International Congress on Thrombosis, Milan, Italy, 6–9 July 2010	Duplicate publication (no additional data)
	Fuji T, Wang CJ, Fujita S, Tachibana S, Kawai Y {Fuji, 2009 #173}	Edoxaban in patients undergoing total hip arthroplasty: a phase Iib dose-finding study [Abstract]	Proceedings of the Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, 5–8 December 2009, Abstract 2098	Pre-2010 (presumably excluded by Uconn)
EMBASE 71208004	Fuji T; Fujita S; Abe Y; Tachibana S; Kawai Y {Fuji, 2013 #174}	Evaluation of edoxaban in Japanese patients with severe renal impairment undergoing lower-limb orthopedic surgery (2013)	Journal of thrombosis and haemostasis : JTH, 2013, 11, 556	Combined TKR and THR
Poster 3320	Fuji T; Fujita S; Tachibana S; Kawai Y; Koretsune Y; Yamashita T; Nakamura M {Fuji, 2010 #175}	Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V trial (2010)	Blood. Conference: 52nd Annual Meeting of the American Society of Hematology, ASH	Duplicate publication (no additional data)
25653574	Fuji T1, Fujita S2, Kawai Y3, Abe Y4, Kimura T5, Fukuzawa M6, Abe K7, Tachibana S8. {Fuji, 2015 #8}	A randomized, open-label trial of edoxaban in Japanese patients with severe renal impairment undergoing lower-limb orthopedic surgery	Thromb J. 2015 Jan 30;13(1):6	No comparison of interest
	Fujisawa M, Naito M, Asayama I, Kambe T, Koga K{Fujisawa, 2003 #176}	Effect of calf-thigh intermittent pneumatic compression device after total hip arthroplasty: Comparative analysis with plantar compression on	Journal of Orthopaedic Science 2003;8(6):807–11	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
		the effectiveness of reducing thrombogenesis and leg swelling		
Abstract P366	Fujita S; Fuji T; Tachibana S; Nakamura M; Kawai Y	Safety and efficacy of edoxaban in patients undergoing hip fracture surgery (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
19684153	Gandhi R, Razak F, Tso P, et al {Gandhi, 2009 #91}	Metabolic syndrome and the incidence of symptomatic deep vein thrombosis following total knee arthroplasty	J Rheumatol 2009;36:2298-301	No intervention of interest
22177437	Ge YY and Cheng JQ and Xi WJ and Xu Y and Kang YM {Ge, 2011 #66}	[Effects of ulinastatin on coagulation function and deep vein thrombosis in patients undergoing hip joint replacement].		No intervention of interest
	Gent M, Hirsh J, Ginsberg JS, et al {Gent, 1996 #178}	Low-molecular-weight heparinoid orgaran is more effective than aspirin in the prevention of venous thromboembolism after urgery for hip fracture	Circulation 1996; 93(1):80–84	Pre-2010 (presumably excluded by Uconn)
20545808	Gerkens S; Crott R; Closon M C; Horsmans Y; Beguin C {Gerkens, 2010 #84}	Comparing the quality of care across Belgian hospitals from medical basic datasets: the case of thromboembolism prophylaxis after major orthopaedic surgery (2010)	J Eval Clin Pract	Combined TKR and THR
23142450	Gesell MW and Gonzalez Della Valle A and Bartolome Garcia S and Memtsoudis SG and Ma Y and Haas SB and Salvati EA {Gesell, 2013 #47}	Safety and efficacy of multimodal thromboprophylaxis following total knee arthroplasty: a comparative study of preferential aspirin vs. routine 13andomiz chemoprophylaxis.	J Arthroplasty 2013 Apr;28(4):575-9	Comparator mixed interventions
22814857	Gillette BP and DeSimone LJ and Trousdale RT and Pagnano MW and Sierra RJ {Gillette, 2013 #53}	Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty.	Clin Orthop Relat Res 2013;471:150–4	Combined TKR and THR
	Glynn O {Glynn, 2002 #179}	The express study: preliminary results	International Journal of Clinical Practice 2003;57(1):57–9	Pre-2010 (presumably excluded by Uconn)
22700784	Gomez-Outes A and Terleira-Fernandez AI and Suarez-Gea ML and Vargas-Castrillon E {Gomez-Outes, 2012 #54}	Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons.		Duplicate publication (no additional data)
	Gomez-Outes A; Terleira-Fernandez A; Suarez-Gea M L; Vargas-Castrillon E	New oral anticoagulants for thromboprophylaxis after total hip or knee replacement: A meta-analysis and indirect treatment comparisons	Basic and Clinical Pharmacology and Toxicology	SR or MA without references (conference abstract)

PubMed ID	Authors	Title	Journal	Rejection Reason
		(2011)		
26194908	Granero J; Diaz de Rada P; Lozano L M; Martinez J; Herrera A {Granero, 2016 #3}	Rivaroxaban versus standard of care in venous thromboembolism prevention following hip or knee arthroplasty in daily clinical practice (Spanish data from the international study XAMOS) (2015)	Revista espanola de cirugia ortopedica y traumatologia	Combined TKR and THR
21870978	Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L {Granger, 2011 #70}	Apixaban versus warfarin in patients with atrial fibrillation	N Engl J Med 2011;365: 981e992	Not population of interest
noPMID 07	Haas S; Turpie A G; Jamal W; Schmidt A; Lassen M; Mantovani L; Kreutz R	XAMOS: A non-interventional study in 17,701 patients undergoing major hip or knee surgery and receiving oral rivaroxaban or conventional regimens for thromboprophylaxis (2013)	Hamostaseologie	Duplicate publication (no additional data)
1447236	Haas SB, Tribus CB, Insall JN, et al{Haas, 1992 #113}	The significance of calf thrombi after total knee arthroplasty	J Bone Joint Surg Br 1992;74:799-802	No comparison of interest
23768996	Hamidi V and Ringerike T and Hagen G and Reikvam A and Klemp M{Hamidi, 2013 #34}	New anticoagulants as thromboprophylaxis after total hip or knee replacement.		Duplicate publication (no additional data)
22480528	Hamilton SC, Whang WW, Anderson BJ, Bradbury TL, Erens GA, Roberson JR{Hamilton, 2012 #57}	Inpatient enoxaparin and outpatient aspirin chemoprophylaxis regimen after primary hip and knee arthroplasty: a preliminary study	J Arthroplasty 2012 Oct;27(9):1594-8	Combined TKR and THR
25224874	Hamilton W G; Reeves J D; Fricka K B; Goyal N; Engh G A; Parks N L{Hamilton, 2015 #11}	Mechanical thromboembolic prophylaxis with risk stratification in total knee arthroplasty (2015)	J Arthroplasty	No comparison of interest
18034323	Happe LE, Farrelly EM, Stanford RH, et al{Happe, 2008 #97}	Cost and occurrence of thrombocytopenia in patients receiving venous thromboembolism prophylaxis following major orthopaedic surgeries	J Thromb Thrombolysis 2008;26:125-31	Combined TKR and THR
23344716	Harenberg J; Weiss C; Marx S; Zolfaghari S{Harenberg, 2013 #42}	Clinical trials with new direct oral anticoagulants: Additive value of indirect comparisons also named	Phlebologie	No primary data

PubMed ID	Authors	Title	Journal	Rejection Reason
		network meta-analyses (2013)		
	Harms M, Engstrom B {Harms, 1991 #180}	Continuous passive motion as an adjunct to treatment in the physiotherapy management of the total knee arthroplasty patient	Physiotherapy 1991;77 (4):301–7	Pre-2010 (presumably excluded by Uconn)
	Harris WH, Athanasoulis CA, Waltman AC, Salzman EW {Harris, 1982 #181}	High and low-dose aspirin prophylaxis against venous thromboembolic disease in total hip replacement	J Bone Joint Surg Am 1982;64(1):63–66	Pre-2010 (presumably excluded by Uconn)
	Hauer W, Sinz G, Hiesser H	Hirudin versus enoxaparin as prophylaxis of venous thromboembolism in patients undergoing total hip replacement	Annals of Hematology 1997;74(Suppl 2):A 130	Pre-2010 (presumably excluded by Uconn)
HTA-32011001330	Hayes; Inc	Pneumatic compression for prevention of deep vein thrombosis following hip surgery (Structured abstract) (2011)	http://www.hayesinc.com/hayes/htareports/directory/pneumatic-compression-for-prevention-of-deep-vein-thrombosis-following-hip-surgery/	No abstract or full text available
EMBASE 71208848	Heckmann M B; Hillebrand I; Silay H; Thermann H; Siebold R; Klonz A; Gruber G; Scheller G; Heckmann F {Heckmann, 2013 #182}	Rivaroxaban superior to Nadroparin for thromboprophylaxis in patients receiving hip or knee arthroplasty (2013)	Journal of thrombosis and haemostasis : JTH, 2013, 11, 822	Combined TKR and THR
26194889	Heckmann, M., Thermann, H., Heckmann, F. {Heckmann, 2015 #254}	Rivaroxaban versus high dose nadroparin for thromboprophylaxis after hip or knee arthroplasty	Hamostaseologie	Could not retrieve
	Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, et al, Astrazeneca Arthroplasty Study Group {Heit, 2001 #183}	Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: A phase 2 dose-finding study	Archives of Internal Medicine 2001;161 (18):2215–21	Pre-2010 (presumably excluded by Uconn)
	Hoek JA, Nurmohamed MT, Hamelynck KJ, et al {Hoek, 1992 #184}	Prevention of deep vein thrombosis following total hip replacement by low molecular weight heparinoid	Thromb Haemost 1992; 67: 28-32	Pre-2010 (presumably excluded by Uconn)
doi: 10.1097/BCO.0000000000000222	Holden, D. N., Maceira, E.	Thromboembolism prophylaxis failure rates after hip and knee arthroplasty: Comparison of aspirin and anticoagulants	Current Orthopaedic Practice	Combined hip and knee; NRCS N<750

PubMed ID	Authors	Title	Journal	Rejection Reason
25972699	Hossain Shahcheraghi G; Javid M; Arasteh M M {Hossain Shahcheraghi, 2015 #5}	Thromboembolic disease after knee arthroplasty is rare in Southern Iran (2015)	J Orthop	nRCS N<750
	Howard A, Zaccagnini D, Ellis M, Williams A, Davies AH, Greenhalgh RM {Howard, 2004 #185}	Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery	British Journal of Surgery 2004;91(7):842–7	Pre-2010 (presumably excluded by Uconn)
19567860	Hu S, Zhang Z-, Hua Y-, et al {Hu, 2009 #92}	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	No comparison of interest
	Huang D, Peng Y, Su P, Ye W, Liang A {Huang, 2003 #186}	The effect of continuous passive motion after total knee arthroplasty on joint function	Chinese Journal of Clinical Rehabilitation 2003;7:1661–2	Pre-2010 (presumably excluded by Uconn)
26182982	Huang, R., Buckley, P. S., Scott, B., Parvizi, J., Purtill, J. J.	Administration of Aspirin as a Prophylaxis Agent Against Venous Thromboembolism Results in Lower Incidence of Periprosthetic Joint Infection	J Arthroplasty	Does not report hip and knee separately
	Hui AC, Heras-Palou C, Dunn I, Triffitt PD, Crozier A, Imeson J, et al {Hui, 1996 #188}	Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement	The Journal of Bone and Joint Surgery, British Volume 1996;78(4):550–4	Pre-2010 (presumably excluded by Uconn)
	Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al{Hull, 2000 #189}	Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a doubleblind, randomized comparison, North American Fragmin Trial Investigators	Arch Intern Med 2000;160:2208–15	Pre-2010 (presumably excluded by Uconn)
noPMID 04	Huo M H; Spencer D L; Borah B J; Mills R M; Fan Y; Yarlas A; Klaskala W {Huo, 2012 #190}	Post-discharge venous thromboembolism and bleeding in a large cohort of patients undergoing total hip or total knee arthroplasty (2012)	Journal of Clinical Outcomes Management	No intervention of interest
Abstract PCV4	Huo M H; Spencer D L; Fan Y; Borah B J; Mills R M; Klaskala W {Huo, 2012 #191}	Thromboprophylaxis and the risk of post-discharge venous thromboembolism and bleeding in patients undergoing total hip or knee arthroplasty (2012)	Value in Health	No intervention of interest
Abstract 0564	Huo M; Eriksson B; Dahl O; Kurth A; Hantel S; Hermansson K; Schnee J;	Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip	Haematologica	Duplicate publication (no additional data)

PubMed ID	Authors	Title	Journal	Rejection Reason
	Friedman R {Huo, 2010 #192}	arthroplasty: The re-novate II 17andomized trial (2010)		
21621959	IJRCW Committee{, 2012 #75}	A prospective comparison of warfarin to aspirin for thromboprophylaxis in total hip and total knee arthroplasty	J Arthroplasty 2012;27:1–9e2	nRCS N<750
21621959	Intermountain Joint Replacement Center Writing Committee.	A prospective comparison of warfarin to aspirin for thromboprophylaxis in total hip and total knee arthroplasty.	J Arthroplasty 2012;27(1):1.	nRCS N<750
25877506	Izumi, M., Migita, K., Nakamura, M., Jiuchi, Y., Sakai, T., Yamaguchi, T., Asahara, T., Nishino, Y., Bito, S., Miyata, S., Kumagai, K., Osaki, M., Mawatari, M., Motokawa, S. {Izumi, 2015 #258}	Risk of venous thromboembolism after total knee arthroplasty in patients with rheumatoid arthritis	J Rheumatol	no medication as control
22832942	Jameson SS and Rymaszewska M and Hui AC and James P and Serrano-Pedraza I and Muller SD{Jameson, 2012 #52}	Wound complications following rivaroxaban administration: a multicenter comparison with low-molecular-weight heparins for thromboprophylaxis in lower limb arthroplasty.		Combined TKR and THR
22253396	Januel JM and Chen G and Ruffieux C and Quan H and Douketis JD and Crowther MA and Colin C and Ghali WA and Burnand B{Januel, 2012 #62}	Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review.		Duplicate publication (no additional data)
21196550	Jensen CD and Steval A and Partington PF and Reed MR and Muller SD{Jensen, 2011 #80}	Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban: a retrospective cohort study.		nRCS N<750
22148001	Ji HM and Lee YK and Ha YC and Kim KC and Koo KH{Ji, 2011 #67}	Little impact of antiplatelet agents on venous thromboembolism after hip fracture surgery.		No intervention of interest
27213284	Jiang, L., Zhang, S., Zhao, Y. {Jiang, 2016 #248}	Stacked Modalities' Thromboprophylactic Therapy for Patients Undergoing Total Knee Replacement Surgery	J Knee Surg	Could not retrieve
	Johnson DP, Eastwood DM {Johnson, 1992 #193}	Beneficial effects of continuous passive motion after total condylar knee arthroplasty	Annals of the Royal College of Surgeons of England 1992;74(6): 412–6	Pre-2010 (presumably excluded by Uconn)
24334158	Jorgensen CC and Jacobsen MK and Soeballe K and Hansen TB and Husted H	Thromboprophylaxis only during 17andomized1717ion in fast-track hip and knee		Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
	and Kjaersgaard-Andersen P and Hansen LT and Laursen MB and Kehlet H {Jorgensen, 2013 #23}	arthroplasty, a prospective cohort study.		
1997063	Jorgensen LN, Rasmussen LS, Nielsen PT, et al {Jorgensen, 1991 #116}	Antithrombotic efficacy of continuous extradural analgesia after knee replacement	Br J Anaesth 1991;66:8-12	No intervention of interest
8384388	Jorgensen PS, Knudsen JB, Broeng L, et al {Jorgensen, 1993 #112}	[The thromboprophylactic effect of low molecular weight heparin (Fragmin) in hip fracture surgery. A placebo controlled trial]	Ugeskr Laeger 1993;155:706-8	Duplicate publication (no additional data)
	Josefsson G, Dahlqvist A, Bodfors B {Josefsson, 1987 #194}	Prevention of thromboembolism in total hip replacement: Aspirin versus dihydroergotamine-heparin	Acta Orthop Scand 1987;58(6):626–629	Pre-2010 (presumably excluded by Uconn)
	Kakkar AK, Brenner B, Dahl OE, et al {Kakkar, 2008 #195}	Extended duration rivaroxaban versus shortterm enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, 18andomized controlled trial	Lancet 2008; 372(9632):31-39	Pre-2010 (presumably excluded by Uconn)
	Kakkar VV, Howes J, Sharma V, Kadziola Z {Kakkar, 2000 #196}	A comparative double-blind, 18andomized trial of a new second generation LMWH (bemiparin) and UFH in the prevention of postoperative venous thromboembolism, The Bemiparin assessment group	Thromb Haemost 2000;83(4):523-529	Pre-2010 (presumably excluded by Uconn)
	Kalodiki E, Gill K, Al-Kutobi, Birch R, Harris N, Hunt D, et al {Kalodiki, 1992 #197}	Low molecular weight heparin with or without graduated elastic compression in deep vein prophylaxis after elective hip replacement	British Journal of Surgery 1992; Vol 79, issue 11:1223	Pre-2010 (presumably excluded by Uconn)
	Kalodiki E, Nicolaides A, Al-Kutoubi A, Birch B, Harris N, Hunt D, et al {Kalodiki, 1993 #198}	Low molecular weight heparin (LMWH) and LMWH plus graduated elastic compression for deep venous thrombosis (DVT) prophylaxis in total hip replacement	Thrombosis and Haemostasis 1993; Vol 69, issue 6:650-Abstract No 387	Pre-2010 (presumably excluded by Uconn)
	Kalodiki E, Nicolaides AN, Al-Kutoubi A, Birch R, Harris N, Hunt D, et al {Kalodiki, 1993 #199}	LMWH and LMWH plus graduated elastic compression for DVT prophylaxis in total hip replacement	Thrombosis and Haemostasis 1993; Vol 69, issue 6:619-Abstract No 270	Pre-2010 (presumably excluded by Uconn)
	Kanan PS, Schwartsmann CR, Boschin LC, Conrad S, Silva MF{Kanan, 2008 #200}	Estudo 18andomized18 entre rivaroxaban e enoxaparina na profilaxia de tromboembolismo venoso profundo em pacientes submetidos à artroplastia total do quadril	Rev Bras Ortop 2008;43(8):319–28	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
21748508	Kang BJ and Lee YK and Kim HJ and Ha YC and Koo KH{Kang, 2011 #72}	Deep venous thrombosis and pulmonary embolism are uncommon in East Asian patients after total hip arthroplasty.		No comparison of interest
26630467	Kaye, I. D., Patel, D. N., Strauss, E. J., Alaia, M. J., Garofolo, G., Martinez, A., Jazrawi, L. M. {Kaye, 2013 #251}	Prevention of Venous Thromboembolism after Arthroscopic Knee Surgery in a Low-Risk Population with the Use of Aspirin. A Randomized Trial	Bull Hosp Jt Dis (2013)	Placebo trial
22858314	Khokhar A and Chari A and Murray D and McNally M and Pandit H{Khokhar, 2013 #51}	Venous thromboembolism and its prophylaxis in elective knee arthroplasty: an international perspective.		Duplicate publication (no additional data)
23683524	Kim G H; Park B Y; Bae T Y; Kang J W; In Y{Kim, 2013 #36}	Can enoxaparin reduce thromboembolism related events after primary TKA in 19ando patients? (2013)	Journal of Arthroplasty	nRCS placebo comparison
12892186	Kim YH, Oh SH, Kim JS{Kim, 2003 #100}	Incidence and natural history of deep-vein thrombosis after total hip arthroplasty. A prospective and 19andomized clinical study	J Bone Joint Surg Br 2003;85:661-5	No intervention of interest
Abstract PII6	Kreutz R; Schmidt A; Turpie A G; Lassen M R; Mantovani L G; Holberg G; Haas S {Kreutz, 2013 #201}	Rivaroxaban or conventional thromboprophylaxis in routine clinical practice in over 17,000 patients undergoing major orthopedic surgery: Impact of co-medications on adverse events (2013)	Clinical Pharmacology and Therapeutics	Duplicate publication (no additional data)
26580706	Kreutz, R., Haas, S., Holberg, G., Lassen, M. R., Mantovani, L. G., Schmidt, A., Turpie, A. G. G. {Kreutz, 2016 #252}	Rivaroxaban compared with standard thromboprophylaxis after major orthopaedic surgery: Co-medication interactions	British Journal of Clinical Pharmacology	Does not report hip and knee separately
21575551	Kucera T and Maly R and Urban K and Sponer P {Kucera, 2011 #77}	[Venous thromboembolism prophylaxis after total hip arthroplasty].	Acta Chir Orthop Traumatol Cech. 2011;78(2):101-5.	nRCS N<750
23796558	Kulshrestha V and Kumar S {Kulshrestha, 2013 #33}	DVT prophylaxis after TKA: routine anticoagulation vs risk screening approach – a randomized study.		nRCS N<750
noPMID 11	Kumar S L V; Rao A S	Prospective study of commonly used prophylactic anticoagulants in arthroplasy patients (2012)	Malaysian Orthopaedic Journal	Combined TKR and THR
	Kurth AA, Dahl OE, van-Dijk CN, Eriksson BI, Frostick SP, Rosencher N, et al {Kurth, 2009 #202}	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(SUPP˙I):7b	Pre-2010 (presumably excluded by Uconn)
23519234	Kwok CS and Pradhan S and Yeong JK and	Relative effects of two different enoxaparin		Duplicate publication (no

PubMed ID	Authors	Title	Journal	Rejection Reason
	Loke YK {Kwok, 2013 #39}	regimens as comparators against newer oral anticoagulants: meta-analysis and adjusted indirect comparison.		additional data)
22220855	Kwong {Kwong, 2012 #63}	Thromboprophylaxis, bleeding and post-operative prosthetic joint infection in total hip and knee arthroplasty: a comprehensive literature review.	Expert Opin Pharmacother	No primary data
23387806	Lalmohamed A and Vestergaard P and Jansen PA and Grove EL and de Boer A and Leufkens HG and van Staa TP and de Vries F {Lalmohamed, 2013 #40}	Prolonged outpatient vitamin K antagonist use and risk of venous thromboembolism in patients undergoing total hip or knee replacement.		No analysis by intevention
	Lalmohamed A; Vestergaard P; Klop C; Bazelier M; De Boer A; De Vries F	Risk of venous thromboembolism in patients with total hip/knee replacements and matched controls: A population-based cohort study in Denmark (2012)	Osteoporosis International	Duplicate publication (no additional data)
Abstract PP400	Lalmohamed A; Vestergaard P; Pouwels S; Klop C; De Boer A; De Vries F {Lalmohamed, 2012 #203}	Risk of venous thromboembolism in patients with total hip/knee replacements and matched controls: A population-based cohort study in Denmark (2012)	Bone	No analysis by intevention
24965841	Laporte S and Chapelle C and Bertoletti L and Lega JC and Cucherat M and Zufferey PJ and Darmon JY and Mismetti P {Laporte, 2014 #15}	Indirect comparison meta-analysis of two enoxaparin regimens in patients undergoing major orthopaedic surgery. Impact on the interpretation of thromboprophylactic effects of new anticoagulant drugs.		Duplicate publication (no additional data)
Abstract OC331	Lassen M R; Agnelli G; Fisher W; George D; Kakkar A; Mismetti P; Mouret P; Lawson F; Turpie A G G	The ultra-low-molecular-weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) after elective knee replacement surgery (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
Abstract OC356	Lassen M R; Gallus A; Raskob G E; Pineo G; Chen D; Ramirez L M {Lassen, 2010 #204}	Randomized double-blind comparison of apixaban and enoxaparin for thromboprophylaxis after hip replacement: The advance-3 trial (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
	Lassen MR, Ageno W, Borris LC, et al {Lassen, 2008 #205}	Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty	N Engl J Med 2008; 358(26):2776-2786	Pre-2010 (presumably excluded by Uconn)
	Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejø Bro HP, Andersen G, et al {Lassen, 1998 #206}	Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty—	Thromb Res 1998;89:281-7	Pre-2010 (presumably excluded by Uconn)

PubMed ID	Authors	Title	Journal	Rejection Reason
		the Danish Prolonged Prophylaxis (DaPP) Study		
	Lassen MR, Dahl OE, Mismetti P, Destree D, Turpie AG {Lassen, 2009 #207}	AVE5026, a new hemisynthetic ultra-low-molecular-weight heparin for the prevention of venous thromboembolism in patients after total knee replacement surgery—TREK: a dose-ranging study	J Thromb Haemost 2009;7(4):566-572	Pre-2010 (presumably excluded by Uconn)
	Lassen MR, Davidson BL, Gallus A, Pineo A, Ansell J, Deitchman D{Lassen, 2003 #208}	A phase II randomized, double-blind, five-arm, parallel-group, dose-response study of a new oral directly-acting factor Xa inhibitor, razaxaban, for the prevention of deep vein thrombosis in knee replacement surgery—on behalf of the razaxaban investigators [Abstract]	Blood 2003;102(11 Pt 1):15a	Pre-2010 (presumably excluded by Uconn)
	Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ {Lassen, 2009 #209}	Apixaban or enoxaparin for thromboprophylaxis after knee replacement	N Engl J Med 2009; 361(6):594-604	Pre-2010 (presumably excluded by Uconn)
8666626	Laupacis A, Rorabeck C, Bourne R, et al {Laupacis, 1996 #109}	The frequency of venous thrombosis in cemented and non-cemented hip arthroplasty	J Bone Joint Surg Br 1996;78:210-2	No intervention of interest
25069387	Lazo-Langner A and Fleet JL and McArthur E and Garg AX {Lazo-Langner, 2014 #13}	Rivaroxaban vs. low molecular weight heparin for the prevention of venous thromboembolism after hip or knee arthroplasty: a cohort study.		Combined TKR and THR
NoPMID 09	Lazo-Langner A; Fleet J L; McArthur E; Garg A X {Lazo-Langner, 2013 #210}	Rivaroxaban versus low molecular weight heparin for the prevention of venous thromboembolism after orthopedic surgery: A population-based study (2013)	Blood. Conference: 55th Annual Meeting of the American Society of Hematology, ASH	No comparison of interest
	Leclerc JR, GeertsWH, Desjardins L, et al {Leclerc, 1992 #211}	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(4):417-423	Pre-2010 (presumably excluded by Uconn)
22066704	Lee C H; Cheng C L; Chang C H; Kao Yang Y H; Lin L J; Lin T C; Yang C Y {Lee, 2012 #69}	Universal pharmacological thromboprophylaxis for total knee arthroplasty may not be necessary in low-risk populations: A nationwide study in Taiwan (2012)	Journal of Thrombosis and Haemostasis	No comparison of interest
23052111	Lee SH and Cho KY and Khurana S and Kim KI {Lee, 2013 #49}	Less blood loss under concomitant administration of tranexamic acid and indirect factor Xa inhibitor following total knee arthroplasty: a prospective		No intervention of interest

PubMed ID	Authors	Title	Journal	Rejection Reason
		randomized controlled trial.		
23112075	Leegwater NC and Willems JH and Brohet R and Nolte PA {Leegwater, 2012 #48}	Cryocompression therapy after elective arthroplasty of the hip.	Hip Int. 2012 Sep-Oct;22(5):527-33	No intervention of interest
1516307	Lemos MJ, Sutton D, Hozack WJ, et al {Lemos, 1992 #114}	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	No comparison of interest
	Lenssen TA, van Steyn MJ, Crijns YH, Waltjé EM, Roox GM, Geesink RJ, et al {Lenssen, 2008 #212}	Effectiveness of prolonged use of continuous passive motion (CPM), as an adjunct to physiotherapy, after total knee arthroplasty	BMC Musculoskeletal Disorders 2008;9:60	Pre-2010 (presumably excluded by Uconn)
10565650	Levy O, Martinowitz U, Oran A, et al {Levy, 1999 #103}	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	No intervention of interest
22489519	Li J and Wu G and Ji WF and Tong PJ {Li, 2012 #56}	[Case-control study on ultra-early application with intermittent pneumatic compression to prevent postoperative deep venous thrombosis of intertrochanteric femoral fracture in elderly patients].	Zhongguo Gu Shang. 2012 Jan;25(1):32-4.	nRCS N<750
9070518	Lieberman JR, Wollaeger J, Dorey F, et al {Lieberman, 1997 #106}	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	No comparison of interest
24154580	Low MH, Yeo SJ, Chin PL, et al. {Low, 2013 #260}	A Singapore perspective on the use of a short course of chemothromboprophylaxis in patients who underwent total knee arthroplasty.	Singapore Med J 2013;54(10):560.	NRCS N<750
	Lynch AF, Bourne RB, Rorabeck CH, Rankin RN, Donald A {Lynch, 1988 #213}	Deep-vein thrombosis and continuous passive motion after total knee arthroplasty	The Journal of Bone and Joint Surgery, American Volume 1988;70(1):11–4	Pre-2010 (presumably excluded by Uconn)
27143213	Malhotra, R., Babhulkar, S., Sanjib, K. B., Clemens, A., Dadi, A., Iyer, R., Kamath, S., Mody, B., Mutha, S., Reddy, G., Shah, V., Shetty, N., Tapasvi, S., Wadhwa, M. {Malhotra, 2016 #249}	Thromboprophylaxis with dabigatran after total hip arthroplasty in Indian patients: A subanalysis of a double-blind, double-dummy, randomized RE-NOVATE II study	Asian J Surg	Subpopulation not of specific interest
	Mantha S{Mantha, 2011 #214}	Oral factor Xa inhibitors vs. enoxaparin for	Journal of Thrombosis	SR or MA without references

PubMed ID	Authors	Title	Journal	Rejection Reason
		thromboprophylaxis after joint replacement surgery: A meta-analysis (2011)	and Haemostasis	(conference abstract)
26520693	Mao, Y. C., Chen, S. T., Chen, C. H., Hsieh, K. P., Gan, K. H. {Mao, 2015 #253}	Rivaroxaban in preventing venous thromboembolism after arthroplastic surgery in Taiwan	Kaohsiung Journal of Medical Sciences	Does not report hip and knee separately
	McInnes J, Larson MG, Daltroy LH, Brown T, Fossel AH, Eaton HM, et al {Mclnnes, 1992 #215}	A controlled evaluation of continuous passive motion in patients undergoing total knee arthroplasty	JAMA 1992;268(11):1423–8	Pre-2010 (presumably excluded by Uconn)
4027101	McKenzie PJ, Wishart HY, Gray I, et al {McKenzie, 1985 #118}	Effects of anaesthetic technique on deep vein thrombosis. A comparison of subarachnoid and general anaesthesia	Br J Anaesth 1985;57:853-7	No intervention of interest
19968601	McNamara I, Sharma A, Prevost T, et al {McNamara, 2009 #90}	Symptomatic venous thromboembolism following a hip fracture	Acta Orthop 2009;80:687-92	No comparison of interest
20424181	Melillo S N; Scanlon J V; Exter B P; Steinberg M; Jarvis C I{Melillo, 2010 #86}	Rivaroxaban for thromboprophylaxis in patients undergoing major orthopedic surgery (2010)	Ann Pharmacother	Duplicate publication (no additional data)
21305339	Merli G J; Malangone E; Lin J; Lamerato L; Stern L{Merli, 2011 #78}	Real-world practices to prevent venous thromboembolism with pharmacological prophylaxis in US orthopedic surgery patients: An analysis of an integrated healthcare database (2011)	Journal of Thrombosis and Thrombolysis	No outcome of interest
25047862	Migita K and Bito S and Nakamura M and Miyata S and Saito M and Kakizaki H and Nakayama Y and Matsusita T and Furuichi I and Sasazaki Y and Tanaka T and Yoshida M and Kaneko H and Abe I and Mine T and Ihara K and Kuratsu S and Saisho K and Miyahara H and Segata T and Nakagawa Y and Kamei M and Torigoshi T and Motokawa S{Migita, 2014 #14}	Venous thromboembolism after total joint arthroplasty: results from a Japanese multicenter cohort study.		nRCS N<750
Abstract O-TU-023	Migita K; Miyata S; Bito S; Nakamura M; Saito M; Nakayama Y; Akimoto H; Matsushita T; Yamada S; Furuichi I; Sasazaki Y; Tanaka T; Yoshida M; Kaneko H; Abe I; Mine T; Ihara K; Kuratsu S;	Seroconversion of anti-PF4/heparin antibodies and its association with deep vein thrombosis in orthopedic surgery patients receiving various thromboprophylaxis methods (2011)	Journal of Thrombosis and Haemostasis	nRCS N<750

PubMed ID	Authors	Title	Journal	Rejection Reason
	Kamei M; Motokawa S {Migita, 2011 #216}			
1864027	Mitchell D, Friedman RJ, Baker JD,3rd, et al {Mitchell, 1991 #115}	Prevention of thromboembolic disease following total knee arthroplasty. Epidural versus general anesthesia	Clin Orthop 1991;(269):109-12	No intervention of interest
7324741	Modig J, Hjelmstedt A, Sahlstedt B, et al {Modig, 1981 #119}	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	No intervention of interest
22134209	Mont MA and Jacobs JJ and Boggio LN and Bozic KJ and Della Valle CJ and Goodman SB and Lewis CG and Yates AJ Jr and Watters WC 3rd and Turkelson CM and Wies JL and Donnelly P and Patel N and Sluka P {Mont, 2011 #68}	Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty.		Duplicate publication (no additional data)
	Montgomery F, Eliasson M {Montgomery, 1996 #217}	Continuous passive motion compared to active physical therapy after knee arthroplasty: similar hospitalization times in a randomized study of 68 patients	Acta Orthopaedica Scandinavica 1996;67(1):7–9	Pre-2010 (presumably excluded by Uconn)
	Mouret P, Eriksson B, Wille-Jorgensen P, Kalebo P, Rosencher N, Bosch P, et al	A comparison of recombination hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement	Annals of Hematology 1998;76(Suppl I):A 11	Duplicate publication (no additional data)
Abstract OC316	Mouret P; Agnelli G; Fisher W; George D; Kakkar A; Lassen M R; Mismetti P; Lawson F; Turpie A G G	The ultra-low-molecular-weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) after elective hip replacement surgery (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
Abstract MO2	Munakata J; Li H; Luo R; Guo Y; O'Sullivan A; Duran A; Nelson M {Munakata, 2013 #218}	Use of real-world evidence (RWE) to validate a trial-based health economic model (2013)	Value in Health	Combined TKR and THR
23852662	Munoa L and Gonzalez AB and Diaz de Rada P and Valenti A and Valenti JR {Munoa, 2014 #32}	Rivaroxaban is as efficient and safe as bemiparin as thromboprophylaxis in knee arthroscopy.		Not surgery of interest
22258781	Nagase Y and Yasunaga H and Horiguchi H and Hashimoto H and Shoda N and Kadono Y and Matsuda S and Nakamura	Risk factors for pulmonary embolism and the effects of fondaparinux after total hip and knee arthroplasty: a retrospective observational study		Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
	K and Tanaka S {Nagase, 2011 #61}	with use of a national database in Japan.		
23682178	Nair V and Kumar R and Singh BK and Sharma A and Joshi GR and Pathak K {Nair, 2013 #37}	Comparative study of extended versus short term thromboprophylaxis in patients undergoing elective total hip and knee arthroplasty in Indian population.		nRCS N<750
	Navarro-Quilis A, Castellet E, Rocha E, Paz-Jimenez J, Planes A {Navarro-Quilis, 2003 #219}	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(3):425-432	Pre-2010 (presumably excluded by Uconn)
2186591	Nielsen PT, Jorgensen LN, Albrecht-Beste E, et al {Nielsen, 1990 #117}	Lower thrombosis risk with epidural blockade in knee arthroplasty	Acta Orthop Scand 1990;61:29-31	No intervention of interest
	Norgren L, Toksvig-Larsen S, Magyar G, et al {Norgren, 1998 #220}	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	Pre-2010 (presumably excluded by Uconn)
21670542	Ogawa S, Shinohara Y, Kanmuri K {Ogawa, 2011 #74}	Safety and efficacy of the oral direct factor Xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation, -The ARISTOTLE-J study-	Circ J. 2011;75(8):1852-9	Not population of interest
	Ohlund C, Fransson SG, Starck SA {Öhlund, 1983 #221}	Calf compression for prevention of thromboembolism following hip surgery	Acta Orthopaedica Scandinavica 1983;54(6):896–9	Pre-2010 (presumably excluded by Uconn)
	Opina A; Golwala H; AbuFadel M; Tafur A{Opina, 2012 #222}	Rivaroxaban is Associated with Higher Incidence of Major Bleeding Compared to Low Molecular Weight Heparin for Venous Thromboembolism Prophylaxis- A Meta-analysis (2012)	Circulation. Conference: American Heart Association	SR or MA without references (conference abstract)
26200403	Ozler T; Ulucay C; Onal A; Altintas F{Ozler, 2015 #2}	Comparison of switch-therapy modalities (enoxaparin to rivaroxaban/dabigatran) and enoxaparin monotherapy after hip and knee replacement (2015)	Acta Orthop Traumatol Turc	Combined TKR and THR
24264881	Parvizi J and Huang R and Raphael IJ and Arnold WV and Rothman RH{Parvizi, 2014 #25}	Symptomatic pulmonary embolus after joint arthroplasty: stratification of risk factors.		Combined TKR and THR
24845718	Parvizi J and Parmar R and Raphael IJ and Restrepo C and Rothman RH{Parvizi, 2014 #16}	Proximal deep venous thrombosis and pulmonary embolus following total joint arthroplasty.		Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
Abstract 972	Patorno E; Bateman B; Choudhry N; Landon J; Schneeweiss S {Patorno, 2013 #223}	Medical and mechanical prophylaxis for venous thromboembolism after total hip and knee replacement (2013)	Pharmacoepidemiology and Drug Safety	No comparison of interest
23594983	Peidro-Garces L and Otero-Fernandez R and Lozano-Lizarraga L {Peidro-Garces, 2013 #38}	[Adherence to and satisfaction with oral outpatient thromboembolism prophylaxis compared to parenteral: SALTO study].		Combined TKR and THR
	Perhoniemi V, Vuorinen J, Myllynen P, et al {Perhoniemi, 1995 #224}	The effect of enoxaparin in prevention of deep venous thrombosis in hip and knee surgery–a comparison with the dihydroergotamine-heparin combination	Ann Chir Gynaecol 1996; 85: 359-363	Pre-2010 (presumably excluded by Uconn)
	Permunian E T; Ageno W; Dentali F; Riva N {Permunian, 2015 #225}	Clinical impact of bleeding complications with direct oral anticoagulants for the prevention of venous thromboembolism in orthopaedic surgery: A systematic review and meta-analysis of randomized controlled trials (2015)	Journal of Thrombosis and Haemostasis	SR or MA without references (conference abstract)
	Peters F, Cohen AT, Agnelli G, Dahl OE, Eriksson BI, Kalebo P	Ximelagatran and its subcutaneous form melagatran, versus enoxaparin as thromboprophylaxis in total hip or total knee replacement	British Journal of Haematology 2003;121(Suppl 1):42	Pre-2010 (presumably excluded by Uconn)
	Pietsch M, Kuhle J, Hamer H, et al {Pietsch, 2002 #226}	Mechanical versus drug prevention of thrombosis after total hip endoprosthesis implantation, A randomized, controlled clinical study	Biomed Tech (Berl) 2003;48:207	Pre-2010 (presumably excluded by Uconn)
11792778	Pitto RP, Hamer H, Fabiani R, et al {Pitto, 2002 #102}	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	No intervention of interest
	Pitto RP, Hamer H, Heiss-Dunlop W, et al {Pitto, 2004 #227}	Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a 26andomized clinical trial	J Bone Joint Surg Br 2004;86:639	Pre-2010 (presumably excluded by Uconn)
9042560	Planes A, Vochelle N, Darmon JY, et al {Planes, 1996 #110}	Efficacy and safety of postdischarge administration of enoxaparin in the prevention of deep venous thrombosis after total hip replacement. A prospective 26andomized double-blind placebo-controlled trial	Drugs 1996;52:47-54	Not population of interest
8684199	Planes A, Vochelle N, Darmon JY, et al	Risk of deep-venous thrombosis after hospital	Lancet 1996;348:224-	Not population of interest

PubMed ID	Authors	Title	Journal	Rejection Reason
	{Planes, 1996 #108}	discharge in patients having undergone total hip replacement: double-blind 27andomized comparison of enoxaparin versus placebo	8	
	Planes A, Vochelle N, Fagola M, Bellaud M {Planes, 1998 #228}	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(6):499-505	Pre-2010 (presumably excluded by Uconn)
	Planes A, Vochelle N, FagolaM, et al {Planes, 1989 #229}	Once-daily dosing of enoxaparin (a low molecular weight heparin) in prevention of deep vein thrombosis after total hip replacement	Acta Chir Scand Suppl 1990;556:108-115	Pre-2010 (presumably excluded by Uconn)
	Porteous MJ, Nicholson EA, Morris LT, James R, Negus D {Porteous, 1989 #230}	Thigh length versus knee length stockings in the prevention of deep vein thrombosis	British Journal of Surgery 1989;76 (3):296–7	Pre-2010 (presumably excluded by Uconn)
22219258	Poultsides LA and Gonzalez Della Valle A and Memtsoudis SG and Ma Y and Roberts T and Sharrock N and Salvati E {Poultsides, 2012 #64}	Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens.		Duplicate publication (no additional data)
Abstract 903	Pratt N; Graves S; Cashman K; Caughey G; Roughead E {Pratt, 2014 #231}	Anti-coagulation after hip or knee joint replacement: Assessment of the benefits and risks in an elderly cohort (2014)	Pharmacoepidemiology and Drug Safety	Insufficient results data reported
25678543	Protty, M. B., Aithal, S., Hickey, B., Rebecca, P., Johansen, A. {Protty, 2015 #259}	Mechanical prophylaxis after hip fracture: What is the risk of deep vein thrombosis? A retrospective observational study	BMJ Open	not comparative - DVT on which hip
Poster 38	Rao N; Agarwal N; Aliga N; Ruroede K; Gnanapragasam G; Tancredi N; Srigiriraju P; Mekheil M; Afolarin H {Rao, 2014 #232}	Safety and effectiveness of anticoagulants in thromboprophylaxis after hip and knee replacement surgery at an inpatient rehabilitation hospital (2014)	PM and R Volume 6, Issue 9, Supplement, Page S195	Combined TKR and THR
26140896	Ramanathan, R., Gu, Z., Limkemann, A. J., Chandrasekhar, S., Rensing, E., Mays, C., Duane, T. M. {Ramanathan, 2015 #256}	Association between interruptions in chemical prophylaxis and VTE formation	American Surgeon	combined medical and surgical admission
23817755	Raphael IJ, Tischler EH, Huang R, et al. {Raphael, 2014 #261}	Aspirin: an alternative for pulmonary embolism prophylaxis after arthroplasty?	Clin Orthop Relat Res 2014;472(2): 492.	combined knee and hip
24269095	Raphael IJ and McKenzie JC and Zmistowski B and Brown DB and Parvizi J and Austin MS {Raphael, 2014 #24}	Pulmonary embolism after total joint arthroplasty: cost and effectiveness of four treatment modalities.		Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
9471929	Ryan DH, Crowther MA, Ginsberg JS, et al {Ryan, 1998 #105}	Relation of factor V Leiden genotype to risk for acute deep venous thrombosis after joint replacement surgery	Ann Intern Med 1998;128:270-6	No intervention of interest
12820078	Sachs RA, Smith JH, Kuney M, et al {Sachs, 2003 #101}	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	nRCS placebo comparison
22592717	Sajid Muhammad S; Desai Mital; Morris Richard W; Hamilton George {Sajid, 2012 #55}	Knee length versus thigh length graduated compression stockings for prevention of deep vein thrombosis in postoperative surgical patients (2012)	Cochrane Database Syst Rev	Not surgery of interest
20393944	Salazar C A; Malaga G; Malasquez G {Salazar, 2010 #87}	Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement (2010)	Cochrane Database Syst Rev	Duplicate publication (no additional data)
21777787	Schade {Schade, 2011 #71}	Antithrombotic pharmacologic prophylaxis use during conservative and surgical management of foot and ankle disorders: a systematic review	Clin Podiatr Med Surg	Not surgery of interest
25529031	Shoda N and Yasunaga H and Horiguchi H and Fushimi K and Matsuda S and Kadono Y and Tanaka S {Shoda, 2015 #10}	Prophylactic effect of fondaparinux and enoxaparin for preventing pulmonary embolism after total hip or knee arthroplasty: A retrospective observational study using the Japanese Diagnosis Procedure Combination database.	Mod Rheumatol. 2015 Jul;25(4):625-9.	Combined TKR and THR
17449088	Shorr AF, Kwong LM, Sarnes M, et al {Shorr, 2007 #98}	Venous thromboembolism after orthopedic surgery: implications of the choice for prophylaxis	Thromb Res 2007;121:17-24	Combined TKR and THR
	Silva Kanan P, Schwartsmann CR, Carbonera Boschin L, Conrad S, Faria Silva M{Kanan, 2008 #233}	Comparative study between rivaroxaban and enoxaparin in deep venous thromboembolism prophylaxis in patients submitted to total hip arthroplasty	Revista Brasileira de Ortopedia 2008;43:319-28	Pre-2010 (presumably excluded by Uconn)
Abstract page 21	Singh S K; Kallhfallah A {Singh, 2012 #234}	The prevent trial-prevention of venous thromboembolism with enoxaparin vs rivaroxaban following hip and knee replacement surgeries (2012)	Internal Medicine Journal	Insufficient results data reported
	Spiro TE, Johnson GJ, Christie MJ, et al	Efficacy and safety of enoxaparin to prevent deep	Ann Intern Med	Pre-2010 (presumably

PubMed ID	Authors	Title	Journal	Rejection Reason
	{Spiro, 1994 #235}	venous thrombosis after hip replacement surgery, Enoxaparin clinical trial group	1994;121(2):81-89	excluded by Uconn)
25946985	Squizzato A and Lussana F and Cattaneo M{Squizzato, 2015 #6}	Post-operative arterial thrombosis with non-vitamin K antagonist oral anticoagulants after total hip or knee arthroplasty.		Duplicate publication (no additional data)
71809411	Squizzato A; Lussana F; Cattaneo M	Incidence of post-operative arterial thrombosis in patients undergoing total hip or total knee arthroplasty treated with non-vitamin K antagonist oral anticoagulants or enoxaparin: A systematic review and a meta-analysis of the literature (2014)	Thrombosis Research	SR or MA without references (conference abstract)
	Squizzato A; Lussana F; Cattaneo M	Post-operative arterial thrombosis with non-vitamin K antagonist oral anticoagulants after total hip or knee arthroplasty: A meta-analysis (2015)	Italian Journal of Medicine	Duplicate publication (no additional data)
23324504	Stewart DW and Freshour JE {Stewart, 2013 #44}	Aspirin for the prophylaxis of venous thromboembolic events in orthopedic surgery patients: a comparison of the AAOS and ACCP guidelines with review of the evidence.		Duplicate publication (no additional data)
24581264	Sun Y and Chen D and Xu Z and Shi D and Dai J and Qin J and Qin J and Jiang Q {Sun, 2014 #19}	Deep venous thrombosis after knee arthroscopy: a systematic review and meta-analysis.		Duplicate publication (no additional data)
24007323	Tahir F; Riaz H; Riaz T; Badshah M B; Riaz I B; Hamza A; Mohiuddin H {Tahir, 2013 #29}	The new oral anti-coagulants and the phase 3 clinical trials – a systematic review of the literature (2013)	Thrombosis Journal	No primary data
	Tamir L, Hendel D, Neyman C, et al{Tamir, 1999 #236}	Sequential foot compression reduces lower limb swelling and pain after total knee arthroplasty	J Arthroplasty 1999;14:333	Pre-2010 (presumably excluded by Uconn)
noPMID 01	Tangelder M	Inhibition of FVIII with TB-402 for the prevention of venous thromboembolism after total knee and hip replacement: Phase I-II results (2013)	Phlebolymphology	No results reported
20383852	Tasker A; Harbord R; Bannister G C {Tasker, 2010 #88}	Meta-analysis of low molecular weight heparin versus placebo in patients undergoing total hip replacement and post-operative morbidity and mortality since their introduction (2010)	Hip Int	Duplicate publication (no additional data)
23328267	Thomas {Thomas, 2013 #43}	Rivaroxaban: an oral factor Xa inhibitor	Clin Ther	No primary data

PubMed ID	Authors	Title	Journal	Rejection Reason
18487854	Thorey F, Stukenborg-Colsman C, Windhagen H, et al {Thorey, 2008 #95}	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	No intervention of interest
	Tian HSF, Zhang K, Liu Y{Tian, 2007 #237}	Efficacy and safety of aspirin in prevention of venous thromboembolism after total joint arthroplasty	Zhonghua Yi Xue Za Zhi 2007;87:3349–52	Pre-2010 (presumably excluded by Uconn)
25547937	Touma L; Filion K B; Atallah R; Eberg M; Eisenberg M J {Touma, 2015 #9}	A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists (2015)	Am J Cardiol	Duplicate publication (no additional data)
26184606	Tsuda, K., Nishii, T., Sakai, T., Takao, M., Nakamura, N., Sugano, N. {Tsuda, 2016 #255}	Thrombophylaxis with low-dose, short-term fondaparinux after elective hip surgery	Journal of Thrombosis and Thrombolysis	NRCS N<750
70266427	Turpie A G G; Agnelli G; Fisher W; George D; Kakkar A; Lassen M R; Mismetti P; Destree D; Mouret P {Turpie, 2014 #26}	Benefit-to-risk profile of the ultra-low-molecularweight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (vte): A meta-analysis of 3 major orthopaedic surgery studies (2010)	Pathophysiology of Haemostasis and Thrombosis	SR or MA without references (conference abstract)
Abstract 20	Turpie A G G; Jamal W; Schmidt A; Lassen M R; Mantovani L G; Kreutz R; Haas S {Turpie, 2012 #238}	XAMOS: A non-interventional study comparing oral rivaroxaban with conventional regimens for thromboprophylaxis after major orthopaedic surgery of the hip and knee (2012)	British Journal of Haematology	Duplicate publication (no additional data)
Abstract 154	Turpie A G G; Schmidt A; Lassen M R; Mantovani L G; Kreutz R; Holberg G; Haas S {Turpie, 2014 #239}	Rivaroxaban for thromboprophylaxis after total hip or knee replacement surgery: Comparison of outcomes of the XAMOS and record studies (2014)	American Journal of Hematology	Duplicate publication (no additional data)
Abstract 500	Turpie A G G; Schmidt A; Lassen M R; Mantovani L; Kreutz R; Holberg G; Haas S {Turpie, 2014 #239}	Rivaroxaban for thromboprophylaxis after total hip or knee replacement surgery: Comparison of outcomes of the XAMOS and record studies (2012)	Blood. Conference: 54th Annual Meeting of the American Society of Hematology, ASH	Duplicate publication (no additional data)
24154549	Turpie AG and Haas S and Kreutz R and Mantovani LG and Pattanayak CW and Holberg G and Jamal W and Schmidt A and van Eickels M and Lassen MR	A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment.	Thromb Haemost. 2014 Jan;111(1):94-102	Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
	{Turpie, 2014 #26}			
	Turpie AG, Bauer KA, Davidson BL, et al {Turpie, 2009 #240}	A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT)	Thromb Haemost 2009; 101(1):68-76	Pre-2010 (presumably excluded by Uconn)
	Turpie AG, et al {Turpie, 2009 #240}	Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial	Lancet 373 (9676) (2009) 1673–1680	Pre-2010 (presumably excluded by Uconn)
	Turpie AG, Gallus AS, Hoek JA {Turpie, 2001 #241}	A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement	N Engl J Med 2001;344(9):619-625	Pre-2010 (presumably excluded by Uconn)
	Turpie AGG, 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 {Turpie, 2005 #242}	J Thromb Haemost 3 (11) (2005) 2479–2486	Pre-2010 (presumably excluded by Uconn)
23355673	Veen Lv and van Raay JJ and Gerritsma-Bleeker CL and Veeger NJ and Hulst Mv {Veen, 2013 #41}	Direct treatment comparison of Dabigatran and Rivaroxaban versus Nadroparin in the prevention of venous thromboembolism after total knee arthroplasty surgery: design of a 31andomized pilot study (DARINA).		No results reported
noPMID 08	Velik-Salchner C; Oswald E; Innerhofer P; Streif W	Thrombin generation during major orthopedic surgery: Rivaroxaban versus enoxaparin for thromboprophylaxis (2011)	Hamostaseologie	Combined TKR and THR
	Venker B; Ruparelia B; Lee E D; Nunley R; Gage B F {Venker, 2012 #243}	Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty (2012)	Pharmacotherapy	SR or MA without references (conference abstract)
Abstract P509	Verhamme P; Verhaeghe R; Ageno W; De Deene A; Glazer S; Prins M; Buller H; Jacquemin M {Verhamme, 2010 #244}	Single intravenous administration of TB-402 for the prophylaxis of VTE after total knee replacement surgery (2010)	Pathophysiology of Haemostasis and Thrombosis	Duplicate publication (no additional data)
	Villasis-Keever M A; Rendon-Masias M E; Mould-Quevedo J F{Villasis-Keever, 2010 #245}	A meta-analysis of efficacy and safety of dalteparin in the prevention and treatment of venous thromboembolic disease (VTE) (2010)	Value in Health	SR or MA without references (conference abstract)
10067997	Wakankar HM, Nicholl JE, Koka R, et al{Wakankar, 1999 #104}	The tourniquet in total knee arthroplasty	J Bone Joint Surg 1999;81-B:30-3	No intervention of interest
24717837	Wang Z and Anderson FA Jr and Ward M and Bhattacharyya T{Wang, 2014 #18}	Surgical site infections and other postoperative complications following prophylactic		Combined TKR and THR

PubMed ID	Authors	Title	Journal	Rejection Reason
		anticoagulation in total joint arthroplasty.		
	Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP {Westrich, 2006 #247}	VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty	J Arthroplasty 2006;21(6 suppl 2):139–143	Pre-2010 (presumably excluded by Uconn)
18751828	Westrich GH, Winiarsky R, Betsy M, et al{Westrich, 2006 #93}	Effect on deep venous thrombosis with flexion during total knee arthroplasty	HSS Journal 2006;2:148-53	No intervention of interest
	Williams JT, Palfrey SM {Williams, 1987 #246}	Cost effectiveness and efficacy of below knee against above knee graduated compression stockings in the prevention of deep vein thrombosis	Phlébologie 1988;41(4):809–11	Pre-2010 (presumably excluded by Uconn)
8895639	Williams-Russo P, Sharrock NE, Haas SB, et al{Williams-Russo, 1996 #107}	Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement	Clin Orthop 1996;:199-208	No intervention of interest
26095331	Wood R C 3rd; Stewart D W; Slusher L; El-Bazouni H; Cluck D; Freshour J; Odle B{Wood, 2015 #4}	Retrospective Evaluation of Postoperative Bleeding Events in Patients Receiving Rivaroxaban After Undergoing Total Hip and Total Knee Arthroplasty: Comparison with Clinical Trial Data (2015)	Pharmacotherapy	No comparison of interest
26026635	Xie, J., Ma, J., Kang, P., Zhou, Z., Shen, B., Yang, J., Pei, F. {Xie, 2015 #257}	Does tranexamic acid alter the risk of thromboembolism following primary total knee arthroplasty with sequential earlier anticoagulation? A large, single center, prospective cohort study of consecutive cases	Thrombosis Research	thromboprophylaxis +/- tranexamic acid
24352825	Yassin M and Mitchell C and Diab M and Senior C{Yassin, 2014 #22}	The necessity of pharmacological prophylaxis against venous thromboembolism in major joint arthroplasty.		Combined TKR and THR

Appendix C. Risk of Bias Assessment

Table C1. RCT risk of bias (total hip replacement)

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Alfaro 1986	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	NR	Low	NR	NR	Low	NR
Andersen 1997	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Anderson 2013	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Unclear	High	Low
Avikainen 1995	Unclear	High	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Bailey 1991	Low	Low	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Barre 1987	Unclear	Unclear	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Borgen 2012	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	High	High
Bramlage 2012	Unclear	Unclear	Low	Low	Low	Unclear	High	High	High	Unclear	Unclear	High	High
Colwell 1994	Low	Low	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Colwell 1999	Unclear	Unclear	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Colwell 2010	Low	High	High	High	Low	Low	Low	High	Low	Unclear	Low	Low	Low
Comp 2001	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Dahl 1997	Unclear	Unclear	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Dechavanne 1989	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Edwards 2008	Unclear	Unclear	High	High	High	Low	Low	NR	Low	NR	NR	Low	NR
Eisele 2006	Unclear	Unclear	Unclear	Unclear	High	Low	Low	High	Unclear	Unclear	High	Low	NR
Eriksson 1991	Unclear	Unclear	Low	Low	Low	High	Low	NR	Low	NR	NR	Low	NR
Eriksson 1996	Unclear	Unclear	Low	Low	High	Low	Low	NR	Low	NR	NR	Low	NR
Eriksson 1997A	Low	Low	Low	Low	High	High	Low	NR	Low	NR	NR	Low	NR
Eriksson 1997B	Unclear	Unclear	Low	Low	High	High	High	NR	Low	NR	NR	Low	NR
Eriksson 2005	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Eriksson 2007B	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Eriksson 2010	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	High	Low	Low
Eriksson 2011	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Unclear	Low	Unclear
Eriksson 2014	Low	Unclear	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Low
Francis 1992	Low	Low	High	High	Low	High	Low	NR	Low	NR	NR	Low	NR
Francis 1997	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Fuji 2008	Unclear	Unclear	Low	Low	High	Low	Low	NR	Low	NR	NR	Low	NR

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Fuji 2014A	Low	High	High	High	Low	High	High	Low	Low	Low	High	Low	Low
Fuji 2014D	Unclear	Unclear	High	High	Unclear	High	High	Low	Low	Unclear	Unclear	High	Low
Fuji 2015	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Low
Hull 1993	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Hull 2000	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Kim 2016	Low	Unclear	Low	Unclear	Low	High	Low	High	Low	Unclear	High	High	Low
Kim 2016A	Low	Unclear	Low	Unclear	Low	High	Low	High	Low	Unclear	High	High	Low
Kalodiki 1996	Low	Low	NR	NR	Low	High	Low	NR	Low	NR	NR	NR	NR
Lassen 1998	Unclear	Unclear	Low	Low	Low	High	Low	NR	Low	NR	NR	Low	NR
Lassen 2002	Low	Low	Low	Low	Low	High	High	NR	Low	NR	NR	Low	NR
Lassen 2010A	Low	Low	Low	Low	Low	High	Mixed*	Low	Low	Low	Low	Low	Low
Lassen 2012	Low	Low	Low	Unclear	Low	High	High	High	Low	Unclear	Unclear	Low	Low
Levine 1991	Unclear	Unclear	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Lieberman 1994	Low	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Lotke 1996	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Menzin 1994	Unclear	Unclear	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Nilsson 1997	Unclear	Unclear	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Paiement 1987	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Planès 1988	Unclear	Unclear	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Planès 1997	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Planès 1999	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Prandoni 2002	Low	Low	Unclear	Unclear	Low	Low	Low	NR	Low	NR	NR	Low	NR
Rader 1998	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Raskob 2010	Low	Low	Low	Low	Low	Unclear	Unclear	High	Low	Unclear	Unclear	Low	Low
Ryan 2002	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Santori 1994	Low	Low	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Schwartsmann 1996	Unclear	Unclear	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Senaran 2006	Unclear	Unclear	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Silbersack 2004	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Stannard 1996	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Stone 1996	Unclear	Unclear	Low	Low	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Turpie 2002	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Verhamme 2013	Unclear	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Unclear	Low	Low	Low
Warwick 1998	Low	Low	High	High	High	Low	Low	NR	Low	NR	NR	Low	NR
Woolson 1991	Low	Low	High	High	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Yokote 2011	Unclear	Unclear	Unclear	Unclear	High	Low	Low	NR	Low	NR	NR	Low	NR
Zhang 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High	High	Unclear	Unclear	Unclear	Low	NR
Zhang 2014	Low	Unclear	High	High	Unclear	Low	Low	High	Unclear	Unclear	Low	Low	NR
Zhirova 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	High

Table C2. RCT risk of bias (total knee replacement)

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Barrellier 2010	Unclear	Low	High	High	High	Low	Low	High	Low	Low	Low	Low	Low
Bauer 2001	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Bonneux 2006	Low	Low	High	High	Unclear	High	Low	NR	Low	NR	NR	Low	NR
Büller 2015	Low	Low	High	High	Low	High	Unclear	Low	Low	Low	High	Low	Low
Choi 2015	Unclear	Unclear	Low	High	High	Low	Low	High	High	Low	Low	Low	NR
Cohen 2013	Unclear	Unclear	Unclear	Unclear	Low	High	High	Low	Low	Low	Unclear	Low	Low
Colwell 1995	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Comp 2001	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Edwards 2008	Unclear	Unclear	High	High	High	Low	Low	NR	Low	NR	NR	Low	NR
Eisele 2006	Unclear	Unclear	Unclear	Unclear	High	Low	Low	High	Unclear	Unclear	High	Low	NR
Eriksson 2005	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Eriksson 2007A	Low	Low	Low	Low	Low	High	Low	NR	Low	NR	NR	Low	NR
Faunø 1994	Low	Low	High	Unclear	High	Low	Low	NR	Low	NR	NR	Low	NR
Fitzgerald 2001	Low	Low	High	High	High	Low	Low	NR	Low	NR	NR	Low	NR
Fuji 2008	Unclear	Unclear	Low	Low	High	Low	Low	NR	Low	NR	NR	Low	NR
Fuji 2010A	Low	Low	Low	Low	High	Unclear	Low	NR	Low	NR	NR	Low	NR
Fuji 2010B	Low	Unclear	Low	Unclear	Low	Low	High	Low	Low	Low	Low	High	Low
Fuji 2014C	Low	Unclear	Low	Low	Low	High	High	Low	Low	Unclear	Unclear	Low	Low
Fuji 2014D	Unclear	Unclear	High	High	Unclear	High	High	Low	Low	Low	Low	High	Low
Ginsberg 2009	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Haas 1990	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Hu 2015	Unclear	Unclear	High	High	Unclear	Low	Low	High	Unclear	Unclear	Unclear	Low	NR
Hull 1993	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Iliopoulos 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear	Unclear	Unclear	Unclear
Jiang 2014	Low	Unclear	High	High	Unclear	Low	Low	High	Low	Unclear	Low	Unclear	Low
Koo 2014	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	High	High	Unclear	Low	Low	NR
Lachiewicz 2004	Low	Low	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Lassen 2007	Low	Low	High	Unclear	Low	Low	Low	NR	Low	NR	NR	Low	NR
Lassen 2010B	Low	Low	Low	Unclear	Low	Low	High	Low	Low	Unclear	Low	High	Low
Lassen 2012	Low	Low	Low	Unclear	Low	High	High	High	Low	Unclear	Unclear	Low	Low

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Leclerc 1996	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Lotke 1996	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Mirdamadi 2014	Low	Unclear	High	High	Low	Low	Low	High	Low	Unclear	Low	Low	Low
Rader 1998	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	NR	Low	NR	NR	Low	NR
Sakai 2016	Low	Unclear	High	High	High	Low	Low	High	Low	Low	Low	Unclear	Low
Silbersack 2004	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR
Verhamme 2011	Low	Low	High	High	Low	Low	Unclear	Low	Low	Low	Low	High	Low
Warwick 2002	Low	Low	High	High	Low	High	Low	NR	Low	NR	NR	Low	NR
Weitz 2010	Unclear	Low	Unclear	Unclear	Low	High	High	Low	Low	Unclear	Low	Low	Low
Westrich 1996	Low	Low	High	High	Low	Low	Low	High	Unclear	Unclear	Low	Low	NR
Westrich 2006	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	High	Low	Low	Low	High	High
Windisch 2011	Unclear	Unclear	High	High	Low	Low	Low	High	Unclear	Unclear	Low	Low	NR
Yilmaz 2015	Low	Unclear	High	High	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear	NR
Zou 2014	Low	High	High	High	Unclear	Low	Low	High	Low	Unclear	Low	Low	Low
NCT00595426	Unclear	Unclear	Low	Low	High	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	High
NCT00246025	Unclear	Unclear	Low	Low	High	Low	Low	Unclear	Unclear	Unclear	Low	Unclear	Low

Table C3. RCT risk of bias (hip fracture surgery)

Study	Adequate generation of a randomized sequence	Allocation concealment	Blinding of PATIENTS	Blinding of PROVIDERS	Blinding of OUTCOME ASSESSORS	Intention-to-treat-analysis	Incomplete results data (attrition bias)	Selective Reporting (reporting bias)	Group similarity at baseline (selection bias)	Compliance with interventions	Outcome assessment timing (across interventions)	Assessment of outcome	Adverse events precisely defined
Eriksson 2001	Low	Low	Low	Low	Low	High	High	NR	Low	NR	NR	Low	NR
Eriksson 2003	Low	Low	Low	Low	Low	Low	Low	NR	Low	NR	NR	Low	NR
Fisher 2013	Low	Low	Low	Low	Low	High	High	High	Low	Low	High	Unclear	Low
Fuji 2014B	Unclear	Unclear	High	High	Unclear	Unclear	High	Low	Low	Low	High	Low	Low
Kennedy 2000	Unclear	Unclear	High	High	Low	High	Low	NR	Low	NR	NR	Low	NR
Lassen 2012	Low	Low	Low	Unclear	Low	High	High	High	Low	Unclear	Unclear	Low	Low
Monreal 1989	Low	Low	Low	Low	Unclear	High	High	NR	Low	NR	NR	Low	NR
Powers 1989	Low	Low	High	High	High	Low	Low	NR	Low	NR	NR	Low	NR
Sasaki 2011	High	High	High	High	Unclear	Low	Low	High	Low	Unclear	Unclear	High	Low
The TIFDED Study Group 1999	Unclear	Unclear	High	High	Low	Low	Low	NR	Low	NR	NR	Low	NR

Table C4. NRCS risk of bias

Author Year PMID Country/Region	Blinding of outcome assessors	Incomplete results data	Selective Reporting	Group similarity at baseline	Compliance with interventions	Outcome assessment timing	Assessment of outcome	Patients selected in equivalent manner	Adverse events precisely defined
Total hip replacement									
Bloch 2014 24395322 UK	High	Low	Low	Unclear	Low	Unclear	Low	Low	Low
Bottle 2015	Unclear	Low	High	Unclear	Low	Low	High	Low	Low
Ishibe 2011 22101618 Japan	High	Low	High	Low	Low	Low	Unclear	Low	Unclear
Jameson 2011 22058295 UK	High	Low	Low	High	Unclear	Low	High	Low	Low
Khatod 2011 22005861 U.S.	Low	Low	High	Low	Low	Low	High	Low	Low
Pedersen 2015 25511580 Denmark	High	Low	Low	Low	Low	Low	High	Low	Low
Vulcano 2012 22684546 U.S.	Low	Low	High	High	High	Low	Low	High	Low

Author Year PMID Country/Region	Blinding of outcome assessors	Incomplete results data	Selective Reporting	Group similarity at baseline	Compliance with interventions	Outcome assessment timing	Assessment of outcome	Patients selected in equivalent manner	Adverse events precisely defined
Wells 2010 21348557 U.S.	Unclear	Unclear	High	High	Low	Low	Unclear	Low	Low
Total knee replacement									
Bloch 2014 24395322 UK	High	Low	Low	Unclear	Low	Unclear	Low	Low	Low
Bottle 2015	Unclear	Low	High	Unclear	Low	Low	High	Low	Low
Bozic 2010 19679434 US	Unclear	Low	NR	High	NR	NR	High	Low	NR
Jameson 2012 22733945 UK	High	Low	Low	High	Unclear	Low	High	Low	Low
Kang 2015 25963358 China	Unclear	Low	High	Unclear	Low	Low	Low	Low	NR
Khatod 2012 21641758 U.S.	Low	Low	High	High	Low	Low	Unclear	Low	Low
Llau 2011 Abstract 6AP3-2 Spain	Unclear	Low	High	Unclear	Low	Low	Unclear	Unclear	NR
Rath 2013 23566737 UK	High	Low	Low	Unclear	Low	Low	Low	Low	Low
Wells 2010 21348557 U.S.	Unclear	Unclear	High	High	Low	Low	Unclear	Low	Low
Hip fracture surgery									
Tsuda 2014 25034972 Japan	High	Low	Low	Low	Low	Unclear	High	Low	High

Appendix D. Study Design and Baseline Characteristics

Table D1. Total hip replacement: Randomized controlled trials

Study	Article Type; Centers	Funding	Percent Female	Mean Age (SD), Years	KQ 1	KQ 2	KQ 3	KQ 4	KQ 6
Alfaro 1986	Peer reviewed publication; Single center	No industry support	47	~64.1 (10.2)			X		
Andersen 1997	Peer reviewed publication; Single center	No industry support	44	~67 (Range 34, 84)			X		
Anderson 2013	Peer reviewed publication; Multicenter	No industry support	43	~57.8 (12)	X				
Avikainen 1995	Peer reviewed publication; Single center	NR	67	~65.5 (Range 27, 86)	X				
Bailey 1991	Peer reviewed publication; Single center	Industry funded	52	~64.9 (41, 88)	X				
Barre 1987	Peer reviewed publication; Unclear	NR	54	~63.2	X				
Borgen 2012	Peer reviewed publication; Single center	NR	65	~68 (8.7)					X
Bramlage 2012	Peer reviewed publication; Multicenter	Industry funded	65	~71.1 (10.1)			X		
Colwell 1994	Peer reviewed publication; Multicenter	Industry funded	51	~65.4 (11.0)	X		X		
Colwell 1999	Peer reviewed publication; Multicenter	Industry funded	56	~64.0 (13.2)	X				
Colwell 2010	Peer reviewed publication; Multicenter	Industry funded	55	~63 (Range 20, 88)	X				
Comp 2001	Peer reviewed publication; Multicenter	Industry funded	50	~63.9 (Range 26, 90)			X		
Dahl 1997	Peer reviewed publication; Multicenter	NR	71	~71.1			X		
Dechavanne 1989	Peer reviewed publication; Multicenter	NR	55	~63.6 (10.7)	X				
Edwards 2008	Peer reviewed publication; Unclear	Industry funded	57	~65.9 (range 31.6, 87.7)				X	
Eisele 2007	Peer reviewed publication; Single center	No industry support	NR	NR				X	
Eriksson 1991	Peer reviewed publication; Unclear	No industry support	58	~68.7 (8.1)	X				
Eriksson 1996	Peer reviewed publication; Multicenter	NR	62	~66.7 (9.8)	X				
Eriksson 1997A	Peer reviewed publication; Multicenter	NR	58	~68.4 (9.6)	X				
Eriksson 1997B	Peer reviewed publication; Multicenter	Industry funded	58	[~66.5 (18, 90)]	X				
Eriksson 2005	Peer reviewed publication; Multicenter	Industry funded	61	~65.9 (range 21, 93)	X				
Eriksson 2007B	Peer reviewed publication; Multicenter	Industry funded	56	~64.0 (10.7)	X				
Eriksson 2010	Peer reviewed publication; Multicenter	Industry funded	53	~60.0 (Range 22, 85)	X				
Eriksson 2011	Peer reviewed publication; Multicenter	Industry funded	52	~62.0 (11.5)	X				
Eriksson 2014	Peer reviewed publication; Multicenter	Industry funded	52	~60.1 (9.0)	X				
Francis 1992	Peer reviewed publication; Multicenter	No industry support	53	~64.0 (12.0)	X				
Francis 1997	Peer reviewed publication; Multicenter	NR	53	~63.0 (13.5)	X				
Fuji 2008	Peer reviewed publication; Multicenter	Industry funded	88	~61.9 (9.7)			X		
Fuji 2014A	Peer reviewed publication; Multicenter	Industry funded	85	60.3 (10.2)	X				
Fuji 2014D	Peer reviewed publication; Multicenter	Industry funded	80	~61.6 (10.7)	X				
Fuji 2015	Peer reviewed publication; Multicenter	Industry funded	86	62.8	X				
Hull 1993	Peer reviewed publication; Multicenter	NR	59	~66.0 (12.0)	X				
Hull 2000	Peer reviewed publication; Multicenter	Industry funded	52	~63.3 (12.7)	X				X
Kalodiki 1996	Peer reviewed publication; Single center	Industry funded	50	~68 (Range 53, 85)	X				
Kim 2016	Peer reviewed publication; Single center	NR	42	44.2 (9.0)	X				
Kim 2016A	Peer reviewed publication; Single center	NR	63	69.0 (6.6)	X				
Lassen 1998	Peer reviewed publication; Multicenter	NR	54	~69.0 (Range 28, 94)			X		
Lassen 2002	Peer reviewed publication; Multicenter	Industry funded	63	~66.5 (Range 24, 97)	X				

Study	Article Type; Centers	Funding	Percent Female	Mean Age (SD), Years	KQ 1	KQ 2	KQ 3	KQ 4	KQ 6
Lassen 2010A	Peer reviewed publication; Multicenter	Industry funded	53	60.8 (Range 19, 93)	X				
Lassen 2012	Peer reviewed publication; Multicenter	Industry funded	54	[~59.5 (19, 90)]		X			
Levine 1991	Peer reviewed publication; Unclear	No industry support	54	~66.5 (9.8)	X				
Lieberman 1994	Peer reviewed publication; Single center	No industry support	58	~66.5 (Range 40, 87)				X	
Lotke 1996	Peer reviewed publication; Unclear	No industry support	61	~66.7	X				
Menzin 1994 8173149	Peer reviewed publication; Multicenter	Industry funded	51	~65.5 (11.0)	X				
Nilsson 1997	Peer reviewed publication; Single center	NR	57	~70 (Range 44-87)			X		
Paiement 1987	Peer reviewed publication; Single center	Industry funded	NR	NR	X				
Planès 1988	Peer reviewed publication; Multicenter	NR	55	~65.8 (10.9)	X				
Planès 1997	Peer reviewed publication; Single center	Industry funded	43	~69.1 (8.7)			X		
Planès 1999	Peer reviewed publication; Multicenter	Industry funded	56	~64.5 (11.0)		X			
Prandoni 2002	Peer reviewed publication; Single center	NR	55	~68.5 (Range 44, 87)			X		
Rader 1998	Peer reviewed publication; Single center	NR	70	~69.0 (12.1)	X				
Raskob 2010	Peer reviewed publication; Multicenter	Industry funded	60	~57.8 (9.8)	X				
Ryan 2002	Peer reviewed publication; Single center	Industry funded	62	~68.8		X			
Santori 1994	Peer reviewed publication; Unclear	NR	74	~71.1 (6.6)	X				
Schwartsmann 1996	Peer reviewed publication; Unclear	NR	59	~60.1 (10.7)	X				
Senaran 2006	Peer reviewed publication; Single center	Industry funded	71	~53.8 (10.0)	X				
Silbersack 2004	Peer reviewed publication; Single center	Industry funded	64	~64.0 (Range 29, 90)				X	
Stannard 1996	Peer reviewed publication; Single center	NR	NR	~67.8 (Range 28, 86)				X	
Stone 1996	Peer reviewed publication; Unclear	NR	64	~64.0 (Range 37, 83)	X				
Turpie 2002	Peer reviewed publication; Multicenter	Industry funded	53	[~67 (Range 18, 92)]	X				
Verhamme 2013	Peer reviewed publication; Multicenter	Industry funded	56	61 (Range 20, 88)	X				
Warwick 1998	Peer reviewed publication; Single center	Industry supplied materials	38	~68 (11)	X				
Woolson 1991	Peer reviewed publication; Single center	No industry support	56	~65.4				X	
Yokote 2011	Peer reviewed publication; Single center	NR	82	~63.3 (11.0)	X				
Zhang 2013	Peer reviewed publication; Single center	NR	43	~64.6 (6.4)	X				
Zhang 2014	Peer reviewed publication; Single center	NR	58	~60.7 (Range 37, 78)			X		
Zhirova 2014	Peer reviewed publication; Unclear	NR	NR	NR	X			X	

Abbreviation list: SD= Standard deviation, KQ= Key question, NR= Not reported

Table D2. Total knee replacement: Randomized controlled trials

Study	Article Type; Centers	Funding	Percent Female	Mean Age (SD), Years	KQ1	KQ2	KQ3	KQ4	KQ6
Barrellier 2010	Peer reviewed publication; Multicenter	NR	63	70			X		
Bauer 2001	Peer reviewed publication; Multicenter	Industry funded	59	~67.5 (10.5)	X				
Bonneux 2006	Peer reviewed publication; Single center	NR	79	~66.3 (9.5)	X				
Büller 2015	Peer reviewed publication; Multicenter	Industry funded	81	~63.2 (8.8)	X		X		
Choi 2015	Peer reviewed publication; Single center	Industry supplied materials	91	70.2 (7.4)			X		
Cohen 2013	Peer reviewed publication; Multicenter	Industry funded	64	~66.9 (Range 28, 88)	X		X		
Colwell 1995	Peer reviewed publication; Multicenter	NR	56	~68.0 (9.2)	X				
Comp 2001	Peer reviewed publication; Multicenter	Industry funded	57	~66.3 (Range 34, 88)			X		
Edwards 2008	Peer reviewed publication; Unclear	Industry funded	56	~68.4 (range 46.4, 88.1)				X	
Eisele 2007	Peer reviewed publication; Single center	No industry support	NR	NR				X	
Eriksson 2005	Peer reviewed publication; Multicenter	Industry funded	61	~65.9 (range 21, 93)	X		X		
Eriksson 2007A	Peer reviewed publication; Multicenter	Industry funded	66	~66.7 (9)	X		X		
Faunø 1994	Peer reviewed publication; Multicenter	Industry funded	61	~70.5 (10.5)	X				
Fitzgerald 2001	Peer reviewed publication; Multicenter	Industry funded	56	~68.1 (9.1)	X				
Fuji 2008	Peer reviewed publication; Multicenter	Industry funded	90	~69.1 (9.1)			X		
Fuji 2010A	Peer reviewed publication; Multicenter	Industry funded	84	~71.6 (7.7)			X		
Fuji 2010B	Peer reviewed publication; Multicenter	Industry funded	79	71.3			X		
Fuji 2014C	Peer reviewed publication; Multicenter	Industry funded	80	72	X				
Fuji 2014D	Peer reviewed publication; Multicenter	Industry funded	88	~72.0 (7.6)	X		X		
Ginsberg 2009	Peer reviewed publication; Multicenter	Industry funded	58	~66.1 (9.5)	X		X		
Haas 1990	Peer reviewed publication; Single center	NR	66	~69.5	X				
Hu 2015	Peer reviewed publication; Single center	NR	45	~61.0 (3.6)	X				
Hull 1993	Peer reviewed publication; Multicenter	NR	59	~66.0 (12.0)	X				
Iliopoulos 2011	Conference abstract; Single center	NR	87	NR	X	X			
Jiang 2014	Peer reviewed publication; Single center	NR	93	~64.5 (7.1)	X				
Koo 2014	Peer reviewed publication; Single center	No industry support	NR	NR			X		
Lachiewicz 2004	Peer reviewed publication; Single center	Industry funded	65	~66.8 (Range 23, 94)			X		
Lassen 2007	Peer reviewed publication; Multicenter	NR	61	~66.7 (range 36, 88)	X				
Lassen 2010B	Peer reviewed publication; Multicenter	Industry funded	73	[~67 (IQR 59, 73)]	X				
Lassen 2012	Peer reviewed publication; Multicenter	Industry funded	71	[~64.5 (Range 22, 88)]		X			
Leclerc 1996	Peer reviewed publication; Multicenter	Industry funded	63	~68.6 (9.3)	X				
Lotke 1996	Peer reviewed publication; Unclear	No industry support	61	~66.7	X				
Mirdamadi 2014	Peer reviewed publication; Single center	NR	58	70 (9)	X				
Rader 1998	Peer reviewed publication; Single center	NR	70	~69.0 (12.1)	X				
Sakai 2016	Peer reviewed publication; Single center	No industry support	83	73.7 (6.7)				X	

Study	Article Type; Centers	Funding	Percent Female	Mean Age (SD), Years	KQ1	KQ2	KQ3	KQ4	KQ6
Silbersack 2004	Peer reviewed publication; Single center	Industry funded	64	~64.0 (Range 29, 90)				X	
Verhamme 2011	Peer reviewed publication; Multicenter	Industry funded	78	65 (Range 38, 81)	X		X		
Warwick 2002	Peer reviewed publication; Single center	NR	65	~72.0 (9.6)	X				
Weitz 2010	Peer reviewed publication; Multicenter	Industry funded	63	~64.5 (Range 38, 90)	X		X		
Westrich 1996	Peer reviewed publication; Single center	No industry support	67	NR				X	
Westrich 2006	Peer reviewed publication; Single center	Industry supplied materials	67	68.9 (10.9)				X	
Windisch 2011	Peer reviewed publication; Single center	NR	NR	~68.5				X	
Yilmaz 2015	Peer reviewed publication; Single center	No industry support	56	~63.6 (6.7)				X	
Zou 2014	Peer reviewed publication; Single center	No industry support	75	~ 64 (Range 47, 82)	X				
NCT00595426	ClinicalTrials.org; Multicenter	Industry funded	53.3 to 64.9	NR	X		X		
NCT00246025	ClinicalTrials.org; Multicenter	Industry funded	83	71.6 (7.5)			X		

Abbreviation list: SD= Standard deviation, KQ= Key question, NR= Not reported

Table D3. Hip fracture surgery: Randomized controlled trials

Study	Article Type; Centers	Funding	Percent Female	Mean Age (SD), Years	KQ1	KQ2	KQ3	KQ4	KQ6
Eriksson 2001	Peer reviewed publication; Multicenter	Industry funded	75	~77.1 (12.5)	X				
Eriksson 2003	Peer reviewed publication; Multicenter	Industry funded	71	[~79 (Range 23, 96)]			X		
Fisher 2013	Peer reviewed publication; Multicenter	Industry funded	64	~71.5 (Range 18, 98)			X		
Fuji 2014B	Peer reviewed publication; Multicenter	Industry funded	80	76.3 (11.2)	X				
Kennedy 2000	Peer reviewed publication; Unclear	NR	52	~76.5	X				
Lassen 2012	Peer reviewed publication; Multicenter	Industry funded	65	[~75.5 (Range 18, 102)]		X			
Monreal 1989	Peer reviewed publication; Unclear	NR	82	~77.0 (11.1)	X				
Powers 1989	Peer reviewed publication; Multicenter	Industry supplied materials	68	~73.7 (Range 43, 90)	X				
Sasaki 2011	Peer reviewed publication; Single center	NR	78	~81.7 (9.0)	X				
The TIFDED Study Group 1999	Peer reviewed publication; Multicenter	No industry support	76	~76.5 (10.5)		X			

Abbreviation list: SD= Standard deviation, KQ= Key question, NR= Not reported

Table D4. Nonrandomized controlled studies

Study	Study design	Funding	Percent female	Mean age (SD)	KQ 1	KQ 3	KQ 4	KQ 6
Total hip replacement								
Bloch 2014{Bloch, 2014 #27}	Peer reviewed publication; Prospective; Single center	No industry support	58	68 (Range 26-93)	X		X	
Bottle 2015	Peer reviewed publication; Retrospective; Single center	NR	60		X		X	
Ishibe 2011{Ishibe, 2011 #42}	Peer reviewed publication; Retrospective; Single center	No industry support	92.0	56.5 (Range 28-80)	X			
Jameson 2011{Jameson, 2011 #43}	Peer reviewed publication; Retrospective; Regional registry	No industry support	60		X			
Khatod 2011{Khatod, 2011 #44}	Peer reviewed publication; Prospective; Regional registry	No industry support	56.9	65.9 (11.8)	X		X	
Pedersen 2015{Pedersen, 2015 #16}	Peer reviewed publication; Prospective; Regional registry	No industry support	56.8	[~69 (Range 10, 80+)]		X		
Vulcano 2012{Vulcano, 2012 #38}	Peer reviewed publication; Retrospective; Single center	No industry support	61.4	63 (13)	X			
Wells 2010{Wells, 2010 #47}	Peer reviewed publication; Retrospective; Regional registry	Industry funded	48	58.14 (10.93)			X	
Total knee replacement								
Bloch 2014{Bloch, 2014 #27}	Peer reviewed publication; Prospective; Single center	No industry support	58	68 (Range 26-93)	X			
Bottle 2015	Peer reviewed publication; Retrospective; Single center	NR	60		X		X	
Bozic 2010{Bozic, 2010 #64}	Peer reviewed publication; Retrospective; Multicenter	No industry support	65	~67.2 (10.4)	X			
Jameson 2012{Jameson, 2012 #36}	Peer reviewed publication; Retrospective; Regional registry	No industry support	57.5		X			
Kang 2015{Kang, 2015 #12}	Peer reviewed publication; Retrospective; Single center	No industry support	63.3	76.8 (11.4)			X	
Khatod 2012{Khatod, 2012	Peer reviewed publication; Prospective; Regional registry	No industry support	63.6	68 (Range 18-101)	X		X	

Study	Study design	Funding	Percent female	Mean age (SD)	KQ 1	KQ 3	KQ 4	KQ 6
#46}								
Llau 2011{Llau, 2011 #164}	Conference abstract; Retrospective; Multicenter	Industry funded						X
Rath 2013{Rath, 2013 #163}	Peer reviewed publication; Prospective; Single center	No industry support	60	68	X		X	
Wells 2010{Wells, 2010 #47}	Peer reviewed publication; Retrospective; Regional registry	Industry funded	62	61.18 (9.41)	X	X		
Hip fracture surgery								
Tsuda 2014{Tsuda, 2014 #21}	Peer reviewed publication; Retrospective; Regional registry	No industry support	80	79.5 (9.4)			X	

Appendix E. Study Arm Details

Table E1. Total hip replacement: Randomized controlled trials

Author Year PMID Country	Arm[†]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
Alfaro 1986 3535158 Spain	Aspirin 500 mg	Antiplatelet	500 mg BID, Oral, 7 days	Preoperative
	Aspirin 125 mg	Antiplatelet	125 mg BID, Oral, 7 days	Preoperative
Andersen 1997 9690480 Denmark	Dalteparin 5-7 days	LMWH	5000 IU qD, SC, 5-7 days	Preoperative stared the evening before surgery
	Dalteparin 35 days	LMWH	5000 IU qD, SC, 35 days	Preoperative stared the evening before surgery
Anderson 2013 23732713 Canada	Dalteparin then Aspirin	LMWH then Antiplatelet	5000 U qD, SC, 10 days	Postoperative started the morning after surgery
	Dalteparin then Aspirin	LMWH then Antiplatelet	81 mg qD, Oral, 28 days	Postoperative
	Dalteparin	LMWH	5000 U qD, SC, 38 days	Postoperative started the morning after surgery
Avikainen 1995 7645915 Finland	Enoxaparin	LMWH	40 mg/0.4 ml BID, SC, 10 days	Preoperative 12 hr
	Heparin	UFH	500 IU BID, SC, 10 days	Preoperative 2 hr
Bailey 1991 1774568 USA	IPC	Mechanical	Continuously except bathing and physical therapy, until discharge	Postoperative immediately after surgery (recovery room)
	Warfarin	VKA	Oral, PT: 14-18 s	Preoperative started the evening before surgery
Barre 1987 2834500 France	Dalteparin	LMWH	2500 anti-Xa U q12h, SC, 10 days	Preoperative 2 hr
	Heparin	UFH	q8h, SC, 10 days	Preoperative 2 hr
Borgen 2012 22476844 Europe	Dalteparin (preop)	LMWH	5000 IU qD, SC, 35 days	Preoperative 12 hr
	Dalteparin (postop)	LMWH	5000 IU qD, SC, 35 days	Postoperative 6 hr
Bramlage 2012 22713698 Germany	Certoparin 5000 IU	LMWH	5000 IU qD, SC, 8-16 days	Preoperative >2 hr
	Certoparin 3000 IU	LMWH	3000 IU qD, SC, 8-16 days	Preoperative >2 hr
Colwell 1994 8288662 USA	Enoxaparin 30 mg q12h	LMWH	30 mg q12h, SC, 7 days	Postoperative <= 24 hr
	Enoxaparin 40 mg qD	LMWH	40 mg qD, SC, 7 days	Postoperative <= 24 hr
	Heparin	UFH	5000 U q8h, SC, 7 days	Postoperative <= 24 hr
Colwell 1999 10428124 USA	Enoxaparin	LMWH	30 mg q12h, SC, until discharge (mean 7.3 days)	Postoperative <= 24 hr
	Warfarin	VKA	Oral, until discharge (mean 7.3 days), INR: 2.0- 3.0	Postoperative <= 24 hr (could be initiated 48h pre-operatively)
Colwell 2010 20194309 USA	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology	Mechanical	20 hr/day, ~11 days	Intraoperative after induction of anesthesia
	Enoxaparin then Enoxaparin	LMWH	30 mg BID, SC, until discharge	Postoperative started the morning after surgery
	Enoxaparin then Enoxaparin	LMWH	40 mg qD, SC, 10 days	Postoperative started on the day of discharge
Comp 2001 11263636 USA	Enoxaparin 7-10 days	LMWH	30 mg BID, SC, 7-10 days	Postoperative 12-24 hr

Author Year PMID Country	Arm[T]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Enoxaparin 7-10 days then 3 weeks	LMWH	30 mg BID, SC, 7-10 days	Postoperative 12-24 hr
	Enoxaparin 7-10 days then 3 weeks	LMWH	40 mg qD, SC, 3 weeks	Postoperative 7-10 days
Dahl 1997 9031444 Norway	Dalteparin 7 days	LMWH	5000 IU qD, SC, 7 days	Preoperative started the evening before surgery
	Dalteparin 35 days	LMWH	5000 IU qD, SC, 35 days	Preoperative started the evening before surgery
Dechavanne 1989 2537787 France	Dalteparin 2500 U q12h	LMWH	2500 anti-Xa U q12h, SC, 10-13 days	Preoperative 2 hr
	Dalteparin 2500 U qD then 5000 U qD	LMWH	2500 anti-Xa U qD, SC, 48 hr	Preoperative 2 hr
	Dalteparin 2500 U qD then 5000 U qD	LMWH	5000 U qD, SC, 10-13 days	Postoperative 48 hr
	Heparin	UFH	dose according to PTT BID, SC, 10-13 days	Preoperative 2 hr
Edwards 2008 18534421 USA	Enoxaparin + IPC	LMWH + Mechanical	30 mg q12h, SC, 7-8 days	Postoperative started the morning after surgery
	Enoxaparin + IPC	LMWH + Mechanical	ActiveCare DVT, till discharge	In the operation room
	Enoxaparin	LMWH	30 mg q12h, SC, 7-8 days	Postoperative started the morning after surgery
Eisele 2007 17473143 Germany	Certoparin + IPC	LMWH + Mechanical	3000 aXa qD, SC, until discharge	Preoperative 12 hr
	Certoparin + IPC	LMWH + Mechanical	6s/session, every 1 min, 1-16 days	NR
	Certoparin	LMWH	3000 aXa qD, SC, until discharge	Preoperative 12 hr
Eriksson 1991 2013587 Sweden	Dalteparin	LMWH	5000 IU qD, SC, 10 days	Preoperative started the evening before surgery
	Heparin	UFH	5000 IU TID, SC, 10 days	Preoperative 2 hr
Eriksson 1996 8596376 Europe	Desirudin	Hirudin	15 mg BID, , 8-11 days	Preoperative after induction of regional block anesthesia
	Heparin	UFH	5000 IU TID, SC, 8-11 days	Preoperative 2 hr
Eriksson 1997A 9070519 Sweden, Denmark	Desirudin	Hirudin	15 mg BID, SC, 8-11 days	Preoperative 30 min (after induction of anesthesia)
	Heparin	UFH	5000 IU TID, SC, 8-11 days	Preoperative 2 hr
Eriksson 1997B 9358126 10 European countries	Desirudin	Hirudin	15 mg BID, SC, 8-12 days	Preoperative 30 min (after induction of regional block anesthesia)
	Enoxaparin	LMWH	40 mg qD, SC, 8-12 days	Preoperative started the evening before surgery
Eriksson 2005 15634273 11 European countries, South Africa	Dabigatran 225 mg BID	DTI	225 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 150 mg BID	DTI	150 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 300 mg qD	DTI	300 mg qD, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 50 mg BID	DTI	50 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Enoxaprin	LMWH	40 mg qD, SC, until venography (6-10 days)	Preoperative 12 hr
Eriksson 2007B 17869635 13	Dabigatran 220mg	DTI	220 mg qD, Oral, 28-35 days	Postoperative 1-4 hr

Author Year PMID Country	Arm[T]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
European countries, Australia, South Africa				
	Dabigatran 150mg	DTI	150 mg qD, Oral, 28-35 days	Postoperative 1-4 hr
	Enoxaparin	LMWH	40 mg qD, SC, 28-35 days	Preoperative started the evening before surgery (post-operative in some countries)
Eriksson 2010 20088935 Europe	Darexaban 120 mg	DTI	120 mg qD, Oral, 5 weeks	Postoperative 6-10 hr
	Darexaban 60 mg	DTI	60 mg qD, Oral, 5 weeks	Postoperative 6-10 hr
	Darexaban 30 mg	DTI	30 mg qD, Oral, 5 weeks	Postoperative 6-10 hr
	Darexaban 10 mg	DTI	10 mg qD, Oral, 5 weeks	Postoperative 6-10 hr
	Darexaban 5 mg	DTI	5 mg qD, Oral, 5 weeks	Postoperative 6-10 hr
	Enoxaparin 40 mg	LMWH	40 mg qD, SC, 5 weeks	Preoperative 12 hr
Eriksson 2011 21225098 19 countries	Dabigatran	DTI	220 mg qD, Oral, 28-35 days	Postoperative 1-4 hr
	Enoxaparin	LMWH	40 mg qD, SC, 28-35 days	Preoperative started the evening before surgery (post-operative in some countries)
Eriksson 2014 24136153 N/S America, Israel, South Africa, India	Darexaban 30 mg BID	DTI	30 mg BID, Oral, 35 days	Postoperative 6-10 hr
	Darexaban 60 mg qD	DTI	60 mg qD, Oral, 35 days	Postoperative 6-10 hr
	Darexaban 15 mg BID	DTI	15 mg BID, Oral, 35 days	Postoperative 6-10 hr
	Darexaban 30 mg qD	DTI	30 mg qD, Oral, 35 days	Postoperative 6-10 hr
	Enoxaparin 40 mg qD	LMWH	40 mg qD, SC, 35 days	Preoperative 12 hr
Francis 1992 1583760 USA	IPC	Mechanical	Continuously while in bed, until venography	Preoperative immediately before surgery (operating room)
	Warfarin	VKA	Oral, until venography, INR 1.5 surgery day, 2.5 post-op	Preoperative 10-14 days
Francis 1997 9314399 USA	Dalteparin	LMWH	5000 IU qD, SC, until venography	Preoperative <=2 hr
	Warfarin	VKA	qD, Oral, until venography, INR: 2.5	Preoperative started the evening before surgery
Fuji 2008 18843459 Japan	Enoxaparin 40 mg qD	LMWH	40 mg qD, SC, 14 days	Postoperative 24-36 hr
	Enoxaparin 20 mg BID	LMWH	20 mg BID, SC, 14 days	Postoperative 24-36 hr
Fuji 2014D 22952213 4 Asian countries	Darexaban 30 mg	FXaI	30 mg BID, Oral, 10–14 days	Postoperative 12-24 hr
	Darexaban 15 mg	FXaI	15 mg BID, Oral, 10–14 days	Postoperative 12-24 hr
	Enoxaparin	LMWH	20 mg (2000 IU) BID (q12h), SC, 10–14 days	Postoperative 24-36 hr
Fuji 2014A 25047458 Japan,Taiwan	Edoxaban 30 mg	FXaI	30 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Edoxaban 15 mg	FXaI	15 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Enoxaparin 20 mg BID	LMWH	20 mg BID, SC, 11-14 days	Postoperative 24-36 hr
Fuji 2015 26269694 Japan	Edoxaban	FXaI	30 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Enoxaparin	LMWH	2000 IU BID, SC, 11-14 days	Postoperative 24-36 hr

Author Year PMID Country	Arm[T]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
Hull 1993 8413432 USA, Canada	Tinzaparin	LMWH	75 IU/kg qD, SC, 14 days§	Postoperative 18-24 hr
	Warfarin	VKA	qD, Oral, 14 days§, INR 2.0-3.0	Preoperative started the evening before surgery
Hull 2000 10904464 USA, Canada	Dalteparin preoperative	LMWH	5000 IU qD, SC	Preoperative 49 min (49)
	Dalteparin postoperative	LMWH	5000 IU qD, SC	Postoperative 6.6 hr (2.4)
	Warfarin	VKA	qD, Oral, INR: 2.0- 3.0	Postoperative started the evening of the surgery
Kalodiki 1996 8803642 NR	Enoxaparin + GCS	LMWH + Mechanical	40 mg qD, SC, until discharge	Preoperative 12 hr
	Enoxaparin + GCS	LMWH + Mechanical	Bilaterally, until discharge	Preoperative
	Enoxaparin	LMWH	40 mg qD, SC, until discharge	Preoperative 12 hr
Kim 2016	Rivaroxaban	FXaI	10 mg, qD, 2 weeks	Postoperative 12 hr
	Enoxaparin	LMWH	40 mg qD, SC, 2 weeks	Postoperative 12 hr
Kim 2016A	Rivaroxaban	FXaI	10 mg, qD, 2 weeks	Postoperative 12 hr
	Enoxaparin	LMWH	40 mg qD, SC, 2 weeks	Postoperative 12 hr
Lassen 1998 9669750 Denmark	Dalteparin 7 days	LMWH	5000 antifactor Xa U qD, SC, 7 days	Preoperative 12 hr
	Dalteparin 42 days	LMWH	5000 antifactor Xa U qD, SC, 42 days	Preoperative 12 hr
Lassen 2002 12049858 16 European countries	Fondaparinux	FXaI	2.5 mg qD, SC, 5-9 days	Postoperative 6 hr (2)
	Enoxaparin	LMWH	40 mg qD, SC, 5-9 days	Preoperative 12 hr (2)
Lassen 2010A 21175312 USA	Apixaban	FXaI	2.5 mg BID, Oral, 34.0 days (7.7) [32-38]	Postoperative 19.0 hr (4.6) [12-24]
	Enoxaparin	LMWH	40 mg qD, SC, 33.9 days (7.8) [32-38]	Preoperative 13.6 hr (2.1) [12±3]
Lassen 2012 22429800 Multinational	Enoxaparin	LMWH	20 or 40 mg qD*, 8.2 days (1.5)	Postoperative 12 hr (1)
	Semuloparin	LMWH	10 or 20 mg qD*, 8.2 days (1.5)	Postoperative 8 hr (1)
Levine 1991 1848054 Canada	Enoxaparin	LMWH	30 mg BID, SC, 14 days‖	Postoperative 12-24 hr
	Heparin	UFH	7500 U BID, SC, 14 days‖	Postoperative 12-24 hr
Lieberman 1994 8126039 USA	Aspirin + IPC	Antiplatelet + Mechanical	325 mg BID, Oral, 3 weeks	Started on the day of surgery
	Aspirin + IPC	Antiplatelet + Mechanical	Continuously, until venogram (postoperative day 6-8)	Postoperative in the recovery room
	Aspirin	Antiplatelet	325 mg BID, Oral, 3 weeks	Started on the day of surgery
Lotke 1996 8595765 USA	Aspirin	Antiplatelet	325 mg BID, Oral, 6 weeks	Preoperative started the day of admission
	Warfarin	VKA	qD, Oral, 6 weeks, PT: 1.2-1.5 X control value	Postoperative started the night of surgery
Menzin 1994 8173149 USA	Enoxaparin 30 mg q12h	LMWH	30 mg q12h, SC, >= 7 days	Postoperative <=24 hr
	Enoxaparin 40 mg qD	LMWH	40 mg qD, SC, >= 7 days	Postoperative <=24 hr

Author Year PMID Country	Arm[T]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Heparin	UFH	5000 U q8h, SC, >= 7 days	Postoperative <=24 hr
Nilsson 1997 9048404 Sweden	Enoxaparin 9 days	LMWH	40 mg qD, SC, 9±2 days	Preoperative 12 hr
	Enoxaparin 30 days	LMWH	40 mg qD, SC, 30±4 days	Preoperative 12 hr
Paiement 1987 3572408 USA	IPC	Mechanical	Continuously, bilateral	Postoperative in the recovery room
	Warfarin	VKA	until at least 2 days after radiographic phlebography, if the result was negative, PTT: 11-12 s	Preoperative started the night before surgery
Planes 1988 2853459 France	Enoxaparin	LMWH	40 mg qD, SC, until 14 days or discharge	Preoperative 12 hr
	Heparin	UFH	5000 IU q8h, SC, until 14 days or discharge	Preoperative 12 hr
Planes 1997 9048403 France	Enoxaparin to discharge	LMWH	40 mg qD, SC, until just before discharge	Preoperative immediately before surgery
	Enoxaparin 21 days post-discharge	LMWH	40 mg qD, SC, until the 21st day after discharge	Preoperative immediately before surgery
Planès 1999 10348714 France	Enoxaparin	LMWH	40 mg qD, SC, 15 days	Preoperative 12 hr
	Tinzaparin	LMWH	4500 antifactor IU Xa qD, SC, 15 days	Preoperative 12 hr
Prandoni 2002 12230419 Italy	Warfarin until hospital discharge	VKA	5 mg qD, Oral, until discharge	Preoperative started the 2nd pre-op day
	Warfarin 28 days	VKA	5 mg qD, Oral, 28 days	Preoperative started the 2nd pre-op day
Rader 1998 9526211 Germany	Heparin then Enoxaparin	UFH then LMWH	5000 IU the night before the operation as well as in the morning and the evening of the operation day, SC, 1 day	Preoperative started the night before surgery
	Heparin then Enoxaparin	UFH then LMWH	40 mg qD, SC, until discharge (mean 16.7 days)	Preoperative started the night before surgery
	Heparin then Heparin	UFH	5000 IU the night before the operation as well as in the morning and the evening of the operation day, SC, 1 day	Preoperative started the night before surgery
	Heparin then Heparin	UFH	5000 IU TID, SC, 3 days; then 7500 IU TID, SC, 1 day, PTT: 40s	Postperative after the first 3 doses
Raskob 2010 20589317 USA, Canada, Russia, 4 European countries	Edoxaban 90 mg	FXaI	90 mg qD, Oral, 7-10 days	Postoperative 6-8 hr
	Edoxaban 60 mg	FXaI	60 mg qD, Oral, 7-10 days	Postoperative 6-8 hr
	Edoxaban 30 mg	FXaI	30 mg qD, Oral, 7-10 days	Postoperative 6-8 hr
	Edoxaban 15 mg	FXaI	15 mg qD, Oral, 7-10 days	Postoperative 6-8 hr
	Dalteparin 5000 IU	LMWH	5000 IU qD, SC, 7-10 days	Postoperative 6-8 hr
Ryan 2002 12429761 USA	IPC	Mechanical	Continuously, until 4-5 days after patient able to stand independently	Postoperative immediately after surgery
	GCS	Mechanical	Continuously, until 4-5 days after patient able to stand independently	Postoperative immediately after surgery
Santori 1994 8027144 Italy	VFP	Mechanical	Continuously, 7-10 days	Postoperative immediately after surgery
	Heparin	UFH	5000 IU TID, SC, 10 days	Preoperative started the day before surgery
Schwartsmann 1996 Embase 1996366023 Brazil	Enoxaparin	LMWH	40 mg qD, SC, 10 days	Postoperative started immediately after surgery

Author Year PMID Country	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Heparin	UFH	5000 IU q8h, SC, 10 days	Postoperative started immediately after surgery
Senaran 2006 16333632 Turkey	Enoxaparin	LMWH	40 mg qD, SC, 7-10 days post-op or until discharge	Preoperative 12 hr
	Heparin	UFH	5000 IU q8h, SC, 7-10 days post-op or until discharge	Preoperative 12 hr
Silbersack 2004 15330019 Germany	Enoxaparin + IPC	LMWH + Mechanical	40 mg qD, SC, until 30 days post–op	Preoperative started the evening before surgery
	Enoxaparin + IPC	LMWH + Mechanical	Continuously, bilateral, until post-op day 10	Postoperative in the recovery room
	Enoxaparin + GCS	LMWH + Mechanical	40 mg qD, SC, until 30 days post–op	Preoperative started the evening before surgery
	Enoxaparin + GCS	LMWH + Mechanical	<= 90 days	Postoperative
Stannard 1996 8640382 USA	Heparin then Aspirin + VFP	UFH then Antiplatelet + Mechanical	5000 U qD, SC, 3 days	NR
	Heparin then Aspirin + VFP	UFH then Antiplatelet + Mechanical	325 mg BID, Oral	NR
	Heparin then Aspirin + VFP	UFH then Antiplatelet + Mechanical	16h/d for first 3 days, 12h/d for the remainder, bilateral	Postoperative immediately after surgery
	Heparin then Aspirin	UFH then Antiplatelet	5000 U qD, SC, 3 days	NR
	Heparin then Aspirin	UFH then Antiplatelet	325 mg BID, Oral	NR
	VFP	Mechanical	16h/d for first 3 days, 12h/d for the remainder, bilateral	Postoperative immediately after surgery
Stone 1996 9049766 UK	IPC	Mechanical	Until discharge or 10 days post-op	Intraoperative the opposite limb, postoperative operated limb
	Enoxaparin	LMWH	40 mg qD, SC, until discharge or 10 days post-op	Preoperative started the evening before surgery
Turpie 2002 12049860 Canada, USA, Australia	Fondaparinux	FXaI	2.5 mg qD, SC, 5-9 days	Postoperative 4-8 hr
	Enoxaparin	LMWH	30 mg BID, SC, 5-9 days	Postoperative 12-24 hr
Verhamme 2013 23615791 8 European countries, Russia	Rivaroxaban 10 mg	FXaI	10 mg qD, Oral, 35 days	Postoperative 6-8 hr
	TB-402 50 mg	FVIII Inhibitor	50 mg‡, IV	Postoperative 2-4 hr
	TB-402 25 mg	FVIII Inhibitor	25 mg‡, IV	Postoperative 2-4 hr
Warwick 1998 9730125 UK	VFP	Mechanical	Continuously, until the 8th post-op day	Postoperative in the recovery room
	Enoxaparin	LMWH	40 mg q24h, SC, untill 8th post-op day	Preoperative 12 hr
Woolson 1991 2013589 USA	Aspirin + IPC	Antiplatelet + Mechanical	650 mg BID, Oral	Preoperative started the evening before surgery
	Aspirin + IPC	Antiplatelet + Mechanical	Bilaterally, until DVT screening	Intraoperative

Author Year PMID Country	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Wafarin + IPC	VKA + Mechanical	Oral, PT: 1.2 to 1.3 X the control	Preoperative started the evening before surgery
	Wafarin + IPC	VKA + Mechanical	Bilaterally, until DVT screening	Intraoperative
	IPC	Mechanical	Bilaterally, until DVT screening	Intraoperative
Yokote 2011 21282767 Japan	Fondaparinux	FXaI	2.5 mg qD, SC, 10 days	Postoperative 18 hr (mean)
	Enoxaparin	LMWH	40 mg qD, SC, 10 days	Postoperative 17 hr (mean)
Zhang 2013 EMBASE 2014592535 China	Rivaroxaban	FXaI	10 mg/d, 5 weeks	Postoperative 6 hr
	LMWH	LMWH	4100 U/d, 2 weeks	Postoperative 6 hr
Zhang 2014 24767296 China	Rivaroxaban 7 days	FXaI	10 mg/d, Oral, 7 days	Postoperative 6-10 hr
	Rivaroxaban 35 days	FXaI	10 mg/d, Oral, 35 days	Postoperative 6-10 hr
Zhirova 2014 25831700 Russia	Enoxaparin + Rivaroxaban	LMWH + FXaI	40 mg	Preoperative 12 hr
	Enoxaparin + Rivaroxaban	LMWH + FXaI	10 mg	NR
	Enoxaparin + Dabigatran	LMWH + DTI	40 mg	Preoperative 12 hr
	Enoxaparin + Dabigatran	LMWH + DTI	220 mg	NR
	Enoxaparin	LMWH	40 mg	Preoperative 12 hr

Abbreviation list: LMWH= Low molecular weight heparin, DTI= Direct thrombin inhibitor, FXaI= Factor Xa inhibitor, UFH= Heparin, unfractionated, VKA= Vitamin K antagonis, FVIII= Factor VIII, FXI= Factor XI, (e)= Enoxaparin, (t)= Tinzaparin, (d)= Dalteparin, INR= International Normalized Ratio, PPT= Partial Thromboplastin Time, PT= Prothrombin Time

* Dose or frequency was determined based on creatinine clearance.

† For studies with more than one treatment modalities in a single arm, each modality is described separately in a single row. The underline indicates which one is described in the row.

‡ Only single dose was provided.

§ Until 14th day postoperatively, venography or discharge.

|| For certain days or until hospital discharge, whichever occurred first.

Table E2. Total knee replacement: Randomized controlled trials

Author Year PMID Country/Region	Arm[†]	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
Barrellier 2010 20797774 France	Anticoagulation (mixed) 10+-2 days	LMWH, FXaI, or UFH	4000 IU (e)/ 5000 IU (d)/ 4500 (t), 11.2 days	Postoperative
	Anticoagulation (mixed) 35+-5 days	LMWH, FXaI, or UFH	4000 IU (e)/ 5000 IU (d)/ 4500 (t), 33.9 days	Postoperative
Bauer 2001 11794149 North America	Fondaparinux	FXaI	2.5 mg qD, SC, till 5th to 9th post-op day	Postoperative 6 hr (2)
	Enoxaparin	LMWH	30 mg BID, SC, till 5th to 9th post-op day	Postoperative 12-24 hr
Bonneux 2006 16387501 Belgium	Fondaparinux	FXaI	2.5 mg qD, 6 weeks	Postoperative 6-12 hr
	Enoxaparin	LMWH	40 mg qD, 6 weeks	Preoperative started the evening before surgery
Büller 2015 25482425 Canada, 4 S/SE European countries	FXI-ASO 300	FXI Inhibitor	300 mg qOD for the 1st week then qW, SC, 39 days	Preoperative 36 days
	FXI-ASO 200	FXI Inhibitor	200 mg qOD for the 1st week then qW, SC, 39 days	Preoperative 36 days
	Enoxaparin	LMWH	40 mg qD, SC, 10 days	Pre or post-operative (depending on investigator)
Choi 2015 24408881 Korea	IPC	Mechanical	90 cycles/h (fixed), 28 sec/cycle, 2 sessions/day, 16.4 days (5.4)	Postoperative started the day of surgery
	IPC	Mechanical	78.9 cycles/h (variable), 12 sec/cycle, 2 sessions/day, 16.4 days (5.4)	Postoperative started the day of surgery
Cohen 2013 23782955 Australia, Canada, Europe, Russia, South Africa, USA	Eribaxaban 10 mg	FXaI	10 mg qD, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 4 mg	FXaI	4 mg qD, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 2.5 mg	FXaI	2.5 mg qD, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 1 mg	FXaI	1 mg qD, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 0.5 mg	FXaI	0.5 mg qD, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 0.3 mg	FXaI	0.3 mg qD, Oral, 6-14 days	Postoperative 6-8 hr
	Eribaxaban 0.1 mg	FXaI	0.1 mg qD, Oral, 6-14 days	Postoperative 6-8 hr
	Enoxaparin 30 mg BID	LMWH	30 mg BID, SC, 6-14 days	Postoperative ~19.3 hr
Colwell 1995 7497668 USA	Enoxaparin	LMWH	30 mg q12h, SC, 7 days	Postoperative <= 8 hr
	Heparin	UFH	5000 U q8h, SC, 7 days	Postoperative <= 8 hr
Comp 2001 11263636 USA	Enoxaparin 7-10 days	LMWH	30 mg BID, SC, 7-10 days	Postoperative 12-24 hr
	Enoxaparin 7-10 days then 3 weeks	LMWH	30 mg BID, SC, 7-10 days	Postoperative 12-24 hr
	Enoxaparin 7-10 days then 3 weeks	LMWH	40 mg qD, SC, 3 weeks	Postoperative 7-10 days
Edwards 2008 18534421 USA	Enoxaparin + IPC	LMWH + Mechanical	30 mg q12h, SC, 7-8 days	Postoperative started the morning after surgery

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Enoxaparin + IPC	LMWH + Mechanical	ActiveCare DVT, till discharge	In the operation room
	Enoxaparin	LMWH	30 mg q12h, SC, 7-8 days	Postoperative started the morning after surgery
Eisele 2007 17473143 Germany	Certoparin + IPC	LMWH + Mechanical	3000 aXa qD, SC, until discharge	Preoperative 12 hr
	Certoparin + IPC	LMWH + Mechanical	6s/session, every 1 min, 1-16 days	NR
	Certoparin	LMWH	3000 aXa qD, SC, until discharge	Preoperative 12 hr
Eriksson 2005 15634273 11 European countries, South Africa	Dabigatran 225 mg BID	DTI	225 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 150 mg BID	DTI	150 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 300 mg qD	DTI	300 mg qD, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Dabigatran 50 mg BID	DTI	50 mg BID, Oral, until venography (6-10 days)	Postoperative 1-4 hr
	Enoxaprin	LMWH	40 mg qD, SC, until venography (6-10 days)	Preoperative 12 hr
Eriksson 2007A 17764540 13 European countries, Australia, South Africa	Dabigatran 220 mg	DTI	220 mg qD, Oral, 6-10 days	Postoperative 1-4 hr
	Dabigatran 150 mg	DTI	150 mg qD, Oral, 6-10 days	Postoperative 1-4 hr
	Enoxaparin	LMWH	40mg qD, SC, 6-10 days	Preoperative started the evening before surgery (post-operative in some countries)
Faunø 1994 7989386 Finland, Denmark	Enoxaparin	LMWH	40 mg qD, SC, 7-10 days	Preoperative started the evening before surgery
	Heparin	UFH	5000 IU TID, SC, 7-10 days	Preoperative started the evening before surgery
Fitzgerald 2001 11407799 NR	Enoxaparin	LMWH	30 mg q12h, SC, 4-14 days	Postoperative <=8 hr after wound closure
	Warfarin	VKA	Oral, 4-14 days, INR: 2-3	Postoperative <=8 hr after wound closure
Fuji 2008 18843459 Japan	Enoxaparin 40 mg qD	LMWH	40 mg qD, SC, 14 days	Postoperative 24-36 hr
	Enoxaparin 20 mg BID	LMWH	20 mg BID, SC, 14 days	Postoperative 24-36 hr
Fuji 2010A 19854610 Japan	Dabigatran 220 mg	DTI	220 mg qD, Oral, 11-14 days	Postoperative >=2 hr after removing indwelling catheter + confirming absence of abnormal bleeding at drainage site
	Dabigatran 150 mg	DTI	150 mg qD, Oral, 11-14 days	Postoperative >=2 hr after removing indwelling catheter + confirming absence of abnormal bleeding at drainage site
Fuji 2010B 20723033 Japan	Edoxaban 60 mg	FXaI	60 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Edoxaban 30 mg	FXaI	30 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Edoxaban 15 mg	FXaI	15 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Edoxaban 5 mg	FXaI	5 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
Fuji 2014D 22952213 3 Asian countries	Darexaban 30 mg	FXaI	30 mg BID, Oral, 10–14 days	Postoperative 12-24 hr
	Darexaban 15 mg	FXaI	15 mg BID, Oral, 10–14 days	Postoperative 12-24 hr

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Enoxaparin	LMWH	20 mg (2000 IU) BID (q12h), SC, 10–14 days	Postoperative 24-36 hr
Fuji 2014C 25294589 Japan, Taiwan	Edoxaban	FXaI	30 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Enoxaparin	LMWH	2000 IU BID, SC, 11-14 days	Postoperative 24-36 hr
Ginsberg 2009 18534438 N/S America, UK	Dabigatran 220 mg	DTI	220 mg qD, Oral, 12-15 days	Postoperative 6-12 hr
	Dabigatran 150 mg	DTI	150 mg qD, Oral, 12-15 days	Postoperative 6-12 hr
	Enoxaparin	LMWH	30 mg BID, SC, 12-15 days	Postoperative 12-24 hr
Haas 1990 2404020 USA	IPC	Mechanical	Continuously, until the morning after lung scan	Preoperative uninvolved limb, postoperative operated limb
	Aspirin	Antiplatelet	650 mg BID, Oral, until discharge	Preoperative started the day before surgery
Hu 2015 No PMID China	Rivaroxaban	FXaI	10 mg qD, Oral, 2 weeks	Postoperative 6 hr
	Enoxaparin	LMWH	5000 U qD, SC, 2 weeks	Preoperative 12 hr
Hull 1993 8413432 USA, Canada	Tinzaparin	LMWH	75 IU/kg qD, SC, 14 days§	Postoperative 18-24 hr
	Warfarin	VKA	qD, Oral, 14 days§, INR: 2.0-3.0	Preoperative started the evening before surgery
Iliopoulos 2011 Abstract P104 Greece	Fondaparinux	FXaI	2.5 mg	Postoperative 6 hr
	Dabigatran	DTI	110 mg	Postoperative 6 hr
	Enoxaparin	LMWH	40 mg	Postoperative 6 hr
	Tinzaparin	LMWH	0.45 mg	Postoperative 6 hr
Jiang 2014 24931228 China	LMWH then rivaroxaban	LMWH then FXaI	5000 U qD, SC, 1-5 days	Postoperative
	LMWH then rivaroxaban	LMWH then FXaI	10 mg qD, Oral, 5-14 days	Postoperative
	Aspirin	Antiplatelet	100 mg qD, Oral, 14 days	Postoperative
Koo 2014 25436073 S Korea	IPC	Mechanical	12 sec/cycle, 2 hours/session, 6 sessions/day	Postoperative
	IPC	Mechanical	11 sec/cycle, 2 hours/session, 6 sessions/day	Postoperative
Lachiewicz 2004 15568526 USA	IPC	Mechanical	>=12-16 h/d, Venaflow	Preoperative contralateral limb (in the OR), postoperative operated limb
	IPC	Mechanical	>=12-16 h/d, Kendal	Preoperative contralateral limb (in the OR), postoperative operated limb
Lassen 2007 17868430 N/S America, Australia, Denmark, Israel, Poland	Enoxaparin	LMWH	30 mg Q12h, SC, 12 +/- 2 days	Postoperative 12-24 hr after skin wound closure
	Warfarin	VKA	5 mg qD, Oral, 12 +/- 2 days	Postoperative started the evening of surgery
Lassen 2010B 20206776 27 countries	Apixaban	FXaI	2.5 mg BID, Oral, 10–14 days	Postoperative 12-24 hr
	Enoxaparin	LMWH	40 mg qD, SC, 10–14 days	Preoperative 12 hr

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
Lassen 2012 22429800 Multinational	Semuloparin	LMWH	10 or 20 mg qD*, 8.3 days (1.7)	Postoperative 8 hr (1)
	Enoxaparin	LMWH	20 or 40 mg qD*, 8.3 days (1.7)	Postoperative 12 hr (1)
Leclerc 1996 8607589 Canada	Enoxaparin	LMWH	30 mg q12h, SC, 14 days‖	Postoperative started the 1st day after surgery
	Warfarin	VKA	qD, 14 days‖, INR 2.0-3.0	Postoperative started the evening of surgery
Lotke 1996 8595765 USA	Aspirin	Antiplatelet	325 mg BID, Oral, 6 weeks	Preoperative started the day of admission
	Warfarin	VKA	qD, Oral, 6 weeks, PT: 1.2-1.5 X control value	Postoperative started the night of surgery
Mirdamadi 2014 25815018 Iran	Dabigatran	DTI	225 mg qD, Oral, 15 days	Postoperative 4 hr
	Enoxaparin	LMWH	40 mg qD, SC, 15 days	Preoperative 12 hr
Rader 1998 9526211 Germany	Heparin then Enoxaparin	UFH then LMWH	5000 IU the night before the operation as well as in the morning and the evening of the operation day, SC, 1 day	Preoperative started the night before surgery
	Heparin then Enoxaparin	UFH then LMWH	40 mg qD, SC, until discharge (mean 16.7 days)	Preoperative started the night before surgery
	Heparin then Heparin	UFH	5000 IU the night before the operation as well as in the morning and the evening of the operation day, SC, 1 day	Preoperative started the night before surgery
	Heparin then Heparin	UFH	5000 IU TID, SC, 3 days; then 7500 IU TID, SC, 1 day, PTT: 40s	Postperative after the first 3 doses
Sakai 2016 26735531	Edoxaban + IPC	FXai + Mechanical	15 mg qD, ~11 days; 1 second compressions of 130 mgHg, 20/minute, 4 days	Postoperative 12 hr
	Edoxaban	FXai	15 mg qD, ~11 days	Postoperative 12 hr
Silbersack 2004 15330019 Germany	Enoxaparin + IPC	LMWH + Mechanical	40 mg qD, SC, until 30 days post–op	Preoperative started the evening before surgery
	Enoxaparin + IPC	LMWH + Mechanical	Continuously, bilateral, until post-op day 10	Postoperative in the recovery room
	Enoxaparin + GCS	LMWH + Mechanical	40 mg qD, SC, until 30 days post–op	Preoperative started the evening before surgery
	Enoxaparin + GCS	LMWH + Mechanical	<= 90 days	Postoperative
Verhamme 2011 21284801 5 European countries, Israel, Russia	Enoxaparin then TB-402 1.2 mg/kg	LMWH then FVIII Ihibitor	40 mg‡, SC	Preoperative started the night before surgery
	Enoxaparin then TB-402 1.2 mg/kg	LMWH then FVIII Ihibitor	1.2 mg/kg‡, IV	Postperative started the day after surgery
	Enoxaparin then TB-402 0.6 mg/kg	LMWH then FVIII Ihibitor	40 mg‡, SC	Preoperative started the night before surgery
	Enoxaparin then TB-402 0.6 mg/kg	LMWH then FVIII Ihibitor	0.6 mg/kg‡, IV	Postperative started the day after surgery
	Enoxaparin then TB-402 0.3 mg/kg	LMWH then FVIII Ihibitor	40 mg‡, SC	Preoperative started the night before surgery
	Enoxaparin then TB-	LMWH then	0.3 mg/kg‡, IV	Postperative started the day after surgery

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	402 0.3 mg/kg	FVIII Ihibitor		
	Enoxaparin	LMWH	40 mg qD, SC, ~11 days	Preoperative started the night before surgery
Warwick 2002 12002490 UK	Enoxaparin	LMWH	40 mg q24h, SC, untill discharge	Preoperative 12 hr
	VFP	Mechanical	Continuously, until discharges	Postoperative in the recovery room
Weitz 2010 20886185 USA, Canada	TAK-442 80 BID	FXaI	80 mg BID, Oral, 10 days	Postoperative 6-8 hr
	TAK-442 40 BID	FXaI	40 mg BID, Oral, 10 days	Postoperative 6-8 hr
	TAK-442 80 qD	FXaI	80 mg qD, Oral, 10 days	Postoperative 6-8 hr
	TAK-442 20 BID	FXaI	20 mg BID, Oral, 10 days	Postoperative 6-8 hr
	TAK-442 40 qD	FXaI	40 mg qD, Oral, 10 days	Postoperative 6-8 hr
	TAK-442 10 BID	FXaI	10 mg BID, Oral, 10 days	Postoperative 6-8 hr
	Enoxaparin	LMWH	30 mg BID, SC, 10 days	Postoperative 12-14 hr
Westrich 1996 8666599 USA	Aspirin+ VFP	Antiplatelet + Mechanical	325 mg BID, Oral, for the study duration	Postoperative started the night of surgery
	Aspirin+ VFP	Antiplatelet + Mechanical	Continuously, until venogram	Postoperative in the recovery room
	Aspirin	Antiplatelet	325 mg BID, Oral, for the study duration	Postoperative started the night of surgery
Westrich 2006 16950076 USA	Enoxaparin + Venoflow	LMWH + Mechanical	30 mg BID, until discharge, then 40 mg qD for 3 weeks	Postoperative 2 hr
	Enoxaparin + Venoflow	LMWH + Mechanical	Entire hospital stay, bilateral	Postoperative in recovery room
	Aspirin + Venoflow	Antiplatelet + Mechanical	325 mg BID, Oral, 4 weeks	Postoperative in recovery room
	Aspirin + Venoflow	Antiplatelet + Mechanical	Entire hospital stay, bilateral	Postoperative in recovery room
Windisch 2011 20652250 Germany	Enoxaparin + VFP	LMWH + Mechanical	40 mg qD, SC, 8 days	Preoperative 24 hr
	Enoxaparin + VFP	LMWH + Mechanical	24 hours	Postoperative in recovery room
	Enoxaparin	LMWH	40 mg qD, SC, 8 days	Preoperative 24 hr
Yilmaz 2015 25852131 Turkey	Enoxaparin + Electrostimulation device (The Geko)	LMWH + Mechanical	1 mg BID, SC, 6 days	Postoperative 6 hr
	Enoxaparin + Electrostimulation device (The Geko)	LMWH + Mechanical	1 hr/session, 6 sessions/day, 6 days	Postoperative
	Enoxaparin	LMWH	1 mg BID, SC, 6 days	Postoperative 6 hr
Zou 2014 24695091 China	Rivaroxaban	FXaI	10 mg qD, Oral, 14 days	Postoperative 12 hr
	Enoxaparin	LMWH	0.4 ml qD, SC, 14 days	Postoperative 12 hr

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
	Aspirin	Antiplatelet	100 mg qD, Oral, 14 days	Postoperative 12 hr
NCT00595426	Wafarin	VKA	Oral, INR 2.0-3.0	ND
	Darexaban 30 mg BID	FXaI	30 mg BID, Oral	ND
	Darexaban 60 mg QD	FXaI	60 mg QD, Oral	ND
	Darexaban 60 mg BID	FXaI	60 mg BID, Oral	ND
	Darexaban 120 mg QD	FXaI	120 mg QD, Oral	ND
NCT00246025	Dabigatran Etexilate 110 mg	DTI	110 mg qD, Oral, 2 weeks	ND
	Dabigatran Etexilate 150 mg	DTI	150 mg qD, Oral, 2 weeks	ND
	Dabigatran Etexilate 220 mg	DTI	220 mg qD, Oral, 2 weeks	ND

Abbreviation list: LMWH= Low molecular weight heparin, DTI= Direct thrombin inhibitor, FXaI= Factor Xa inhibitor, UFH= Heparin, unfractionated, VKA= Vitamin K antagonis, FVIII= Factor VIII, FXI= Factor XI, (e)= Enoxaparin, (t)= Tinzaparin, (d)= Dalteparin, INR= International Normalized Ratio, PPT= Partial Thromboplastin Time, PT= Prothrombin Time

* Dose or frequency was determined based on creatinine clearance.

† For studies with more than one treatment modalities in a single arm, each modality is described separately in a single row. The underline indicates which one is described in the row.

‡ Only single dose was provided.

§ Until 14th day postoperatively, venography or discharge.

|| For certain days or until hospital discharge, whichever occurred first.

Table E3. Hip fracture surgery: Randomized controlled trials

Author Year PMID Country/Region	Arm†	Class	Drug dose, route, duration, INR/PTT/PT	Initiation time
Eriksson 2001 11794148 21 countries	Fondaparinux	FXaI	2.5 mg qD, SC, 5-9 days	Postoperative 6 hr (2) (if surgery was on time) or 12 hr (2) (if surgery was delayed)
	Enoxaparin	LMWH	40 mg qD, SC, 5-9 days	Preoperative 12 hr (2)
Eriksson 2003 12796070 Europe and South America	Fondaparinux 6-8 days	FXaI	2.5 mg qD, SC, 6-8 days	Started <2 hr after randomization
	Fondaparinux 25-31 days	FXaI	2.5 mg qD, SC, 25-31 days	Started <2 hr after randomization
Fisher 2013 23539696 Multinational	Semuloparin 8 days	LMWH	20 mg qD, SC, ~7.9 days	Postoperative 8 hr
	Semuloparin 28 days	LMWH	20 mg qD, SC, ~27.8 days	Postoperative 8 hr
Fuji 2014B 24680549 Japan	Edoxaban	FXaI	30 mg qD, Oral, 11-14 days	Postoperative 6-24 hr
	Enoxaparin	LMWH	2000 IU BID, SC, 11-14 days	Postoperative 24-36 hr
Kennedy 2000 10697085 NR	VFP	Mechanical	>=18 h/d, until the patient was fully ambulatory	Postoperative in the recovery room
	Aspirin	Antiplatelet	325 mg BID, Oral	Postoperative started the surgery day (as soon as the patient was able to tolerate pills orally)
Lassen 2012 22429800 HFx Multinational	Enoxaparin	LMWH	20 or 30 mg qD*, 8.4 days (1.6)	Postoperative 12 hr (1)
	Semuloparin	LMWH	10 or 20 mg qD*, 8.4 days (1.6)	Postoperative 8 hr (1)
Monreal 1989 2544742 Spain	Dalteparin	LMWH	5000 U qD, SC, 9 days	Preoperative 2 hr
	Heparin	UFH	5000 U q8h, SC, 9 days	Preoperative 2 hr
Powers 1989 2650646 Canada	Aspirin	Antiplatelet	650 mg BID, Oral, 21 days||	Postoperative
	Warfarin	VKA	10 mg , Oral, 21 days||	Postoperative
Sasaki 2011 21293896 Japan	Fondaparinux	FXaI	1.5 or 2.5 mg qD*, SC, 14 days	Postoperative started the day after surgery
	Enoxaparin	LMWH	2000 IU qD or BID*, SC, 14 days	Postoperative started the day after surgery
The TIFDED Study Group 1999 10844404 4 European countries	Dalteparin	LMWH	5000 U qD, SC, 9-11 days	Preoperative 2 hr
	Enoxaparin	LMWH	40 mg qD, SC, 9-11 days	Preoperative the last preoperative dose at 2 hr before surgery

Abbreviation list: LMWH= Low molecular weight heparin, DTI= Direct thrombin inhibitor, FXaI= Factor Xa inhibitor, UFH= Heparin, unfractionated, VKA= Vitamin K antagonis, FVIII= Factor VIII, FXI= Factor XI, INR= International Normalized Ratio, PPT= Partial Thromboplastin Time, PT= Prothrombin Time

* Dose or frequency was determined based on creatinine clearance.

† For studies with more than one treatment modalities in a single arm, each modality is described separately in a single row. The underline indicates which one is described in the row.

|| For certain days or until hospital discharge, whichever occurred first.

Table E4. Nonrandomized controlled studies

Author Year PMID Country/Region	Arm	Drug dose, route, duration	Device/IVC filter duration	Initiation time
Total hip replacement				
Bloch 2014 24395322 UK	LMWH			
	LMWH + aspirin (antiplatelet)			
	Dabigatran (DTI)	220 mg qD		Four hours after surgery
Bottle 201510.1016/j.artd.2015.03.004	Aspirin			
	Rivaroxaban, Apixaban, Dabigatran			
	LMWH (standard duration)			
	LMWH (extended duration)			
Ishibe 2011 22101618 Japan	Fondaparinux (FXaI) + mechanical	2.5 mg qD	Mechanical: 3 h/day for several days	Postoperative immediately after surgery
	Enoxaparin (LMWH) + mechanical	20 mg BID	Mechanical: 3 h/day for several days	Postoperative immediately after surgery
Jameson 2011 22058295 UK	Aspirin (antiplatelet)			
	LMWH			
Khatod 2011 22005861 U.S.	compression stockings (mechanical, passive)			
	SCD or VFP (mechanical, active)			
	Aspirin (antiplatelet)			
	aspirin (antiplatelet) + mechanical			
	aspirin (antiplatelet) +/- mechanical			
	Coumadin (warfarin)			
	coumadin (warfarin) + mechanical			
	coumadin (warfarin) +/- mechanical			
	LMWH			
	LMWH + mechanical			
	LMWH +/- mechanical			
Pedersen 2015 25511580 Denmark	Anticoagulation (mixed) Short duration (0-6 days)	6 days		
	Anticoagulation (mixed) Standard duration (7-27 days)	27 days		
	Anticoagulation (mixed) Extended duration (>=28 days)	28+ days		
Vulcano 2012 22684546 U.S.	Aspirin (antiplatelet)	325 mg, BID, oral, 6 weeks		Postoperative started the night of surgery
	Warfarin	5 mg, INR goal = 2, 6 weeks		Postoperative started the night of surgery
Wells 2010 21348557 U.S.	Anticoagulation (mixed) 1-14 days			

Author Year PMID Country/Region	Arm	Drug dose, route, duration	Device/IVC filter duration	Initiation time
	Anticoagulation (mixed) >14 days			
	Anticoagulation (mixed) 1-21 days			
	Anticoagulation (mixed) >21 days			
	Anticoagulation (mixed) 1-28 days			
	Anticoagulation (mixed) >28 days			
Total knee replacement				
Bloch 2014 24395322 UK	LMWH			
	LMWH + aspirin (antiplatelet)			
	Dabigatran (DTI)	220 mg qD		Four hours after surgery
Bottle 2015 10.1016/j.artd.2015.03.004	Aspirin			
	Rivaroxaban, Apixaban, Dabigatran			
	LMWH (standard duration)			
	LMWH (extended duration)			
Bozic 2010 19679434 US	Warfarin			
	Aspirin (antiplatelet)			
Jameson 2012 22733945 UK	Aspirin (antiplatelet)			
	LMWH			
Kang 2015 25963358 China	foot pump (mechanical, active) + LMWH			
	LMWH			
Khatod 2012 21641758 U.S.	compression stockings (mechanical, passive)			
	SCD or VFP (mechanical, active)			
	Aspirin (antiplatelet)			
	aspirin (antiplatelet) + mechanical			
	aspirin (antiplatelet) +/- mechanical			
	Coumadin (warfarin)			
	coumadin (warfarin) + mechanical			
	coumadin (warfarin) +/- mechanical			
	LMWH			
	LMWH + mechanical			
	LMWH +/- mechanical			
Llau 2011 Abstract 6AP3-2 Spain	Enoxaparin (LMWH) (start before)			Preoperative 12 hours
	Enoxaparin (LMWH) (start after)			Postoperative 6-12 hours
Rath 2013 23566737 UK	Rivaroxaban (FXaI)	10 mg, 14 days		Postoperative 6-12 hours
	aspirin (antiplatelet) +/- enoxaparin (LMWH)	aspirin 150 mg, enoxaparin		

Author Year PMID Country/Region	Arm	Drug dose, route, duration	Device/IVC filter duration	Initiation time
		40 mg, qD, 6 weeks		
Wells 2010 21348557 U.S.	Anticoagulation (mixed) 1-14 days			
	Anticoagulation (mixed) >14 days			
	Anticoagulation (mixed) 1-21 days			
	Anticoagulation (mixed) >21 days			
	Anticoagulation (mixed) 1-28 days			
	Anticoagulation (mixed) >28 days			
Hip fracture surgery				
Tsuda 2014 25034972 Japan	Mechanical			
	Mechanical + fondaparinux (FXaI)			

Abbreviation list: qD = daily, LMWH = low molecular weight heparin; SCD = Sequential Compression Device; TED = Thromboembolic Deterrent; VFP = venous foot pump; PMID = PubMed ID; DTI = Direct thrombin inhibitor: FXaI = Factor Xa Inhibitor;

Appendix F. Study Results

Table F1. RCT total hip replacement

Study	Arm	Timepoint	n/N (%)
Adherent/Compliant			
Fuji 2014A 25047458	Edoxaban 30 mg (NA)	11-14 days	85/85 (100%)
	Edoxaban 15 mg (NA)		89/89 (100%)
	Enoxaparin 20 mg BID (NA)		83/87 (95%)
Lassen 2010A 21175312	Apixaban (NA)	~34 days	2595/2626 (99%)
	Enoxaparin (NA)		2647/2659 (100%)
Bleeding, Fatal			
Bailey 1991 1774568	IPC (Mechanical)	Post-operative days	0/50 (0%)
	Warfarin (VKA)		0/45 (0%)
Barre 1987 2834500	Dalteparin (LMWH)	60 days	0/40 (0%)
	Heparin (UFH)		0/40 (0%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	0/211 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/224 (0%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	35 days	0/134 (0%)
	Dalteparin 7 days (NA)		0/131 (0%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/65 (0%)
	Enoxaparin (LMWH)		0/59 (0%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	0/67 (0%)
	Heparin (UFH)		0/69 (0%)
Eriksson 1996 8596376	Desirudin (DTI)	post-operative days	0/202 (0%)
	Heparin (UFH)		0/229 (0%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	0/180 (0%)
	Heparin (UFH)		0/180 (0%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	1/1163 (0.1%)
	Dabigatran 220mg (DTI)		1/1146 (0.1%)
	Enoxaparin (LMWH)		0/1154 (0%)

Study	Arm	Timepoint	n/N (%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	0/1010 (0%)
	Enoxaparin (LMWH)		0/1003 (0%)
Francis 1992 1583760	IPC (Mechanical)	Post-operative days	0/98 (0%)
	Warfarin (VKA)		0/103 (0%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	Post-operative days	0/398 (0%)
	Warfarin (VKA)		0/397 (0%)
Hull 2000 10904464	Warfarin (VKA)	Post-operative days	0/489 (0%)
	Dalteparin preoperative (NA)		0/496 (0%)
	Dalteparin postoperative (LMWH)		0/487 (0%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	0/1140 (0%)
	Enoxaparin (LMWH)		0/1133 (0%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	0/2673 (0%)
	Enoxaparin (LMWH)		0/2659 (0%)
Lassen 2012 22429800 THA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days	0/1153 (0%)
	Enoxaparin (NA)		0/1155 (0%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	0/332 (0%)
	Enoxaparin (LMWH)		0/333 (0%)
Lieberman 1994 8126039	Aspirin (Antiplatelet)	Post-operative days	0/118 (0%)
	Aspirin+IPC (Antiplatelet_Mechanical)		0/113 (0%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	90 days	0/131 (0%)
	Enoxaparin 30 days (NA)		0/131 (0%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	0/108 (0%)
	Enoxaparin (LMWH)		0/120 (0%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	0/85 (0%)
	Enoxaparin to discharge (NA)		0/88 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	0/251 (0%)
	Enoxaparin (NA)		0/248 (0%)

Study	Arm	Timepoint	n/N (%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	90 days	0/184 (0%)
	Warfarin until hospital discharge (NA)		0/176 (0%)
Sakai 2016 26735531	Edoxaban	28 days	0/62 (0)
	Edoxaban + foot pump		0/58 (0)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	0/84 (0%)
	Enoxaparin (LMWH)		0/85 (0%)
Santori 1994 8027144	VFP (Mechanical)	42 days	0/67 (0%)
	Heparin (UFH)		0/65 (0%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	0/47 (0%)
	Enoxaparin (LMWH)		0/52 (0%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		0/50 (0%)
Sørensen 1990 1966794	Placebo (Placebo)	Post-operative days	0/33 (0%)
	Tinzaparin (LMWH)		0/31 (0%)
Stannard 1996 8640382	VFP (PlexiPulse) (NA)	Post-operative days	0/25 (0%)
	VFP (PlexiPulse)+ Heparin then Aspirin (NA)		0/25 (0%)
	Heparin then Aspirin (NA)		0/25 (0%)
Tørholm 1991 1670445	Placebo (Placebo)	Post-operative days	0/54 (0%)
	Dalteparin (LMWH)		0/58 (0%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	1/50 (2.0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	0/1126 (0%)
	Enoxaparin (LMWH)		0/1128 (0%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	0/147 (0%)
	Enoxaparin (LMWH)		0/143 (0%)
Bleeding, Leading to infection			
Verhamme 2013 23615791	TB-402 50 mg (NA)	35 days	1/208 (0.5%)
Verhamme 2013 23615791	TB-402 25 mg (NA)	35 days	2/207 (1.0%)

Study	Arm	Timepoint	n/N (%)
Verhamme 2013 23615791	Rivaroxaban 10 mg (NA)	35 days	0/207 (0%)
Bleeding, Leading to reoperation			
Borgen 2012 22476844	Dalteparin (postop) (NA)	~8 days	0/40 (0%)
	Dalteparin (preop) (NA)		1/40 (2.5%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	5/247 (2.0%)
	Certoparin 5000 IU (NA)		4/232 (1.7%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	0/67 (0%)
	Heparin (UFH)		0/69 (0%)
Eriksson 1996 8596376	Desirudin (DTI)	Post-operative days	4/277 (1.4%)
	Heparin (UFH)		2/277 (0.7%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	0/225 (0%)
	Heparin (UFH)		0/220 (0%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	3/1163 (0.3%)
	Dabigatran 220mg (DTI)		2/1146 (0.2%)
	Enoxaparin (LMWH)		3/1154 (0.3%)
Francis 1992 1583760	IPC (Mechanical)	Post-operative days	0/98 (0%)
	Warfarin (VKA)		0/103 (0%)
Francis 1997 9314399	Dalteparin (LMWH)	Post-operative days	1/271 (0.4%)
	Warfarin (VKA)		0/279 (0%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	5/1140 (0.4%)
	Enoxaparin (LMWH)		3/1133 (0.3%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	1/2673 (0.04%)
	Enoxaparin (LMWH)		1/2659 (0.04%)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	0/75 (0%)
	Enoxaparin (LMWH)		0/78 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	2/1128 (0.2%)
	Enoxaparin (LMWH)		2/1129 (0.2%)
Bleeding, Major			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	1/133 (0.8)

Study	Arm	Timepoint	n/N (%)
	Dabigatran Etexilate 150 mg		0/126 (0)
	Dabigatran Etexilate 220 mg		3/129 (2.3)
Anderson 2013 23732713	Dalteparin (NA)	~100 days	1/400 (0.3%)
	Dalteparin then Aspirin (NA)		0/385 (0%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	3/252 (1.2%)
	Certoparin 5000 IU (NA)		9/248 (3.6%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative days	3/203 (1.5%)
	Enoxaparin 30 mg (NA)		8/195 (4.1%)
	Heparin (UFH)		13/209 (6.2%)
Colwell 1999 10428124	Warfarin (VKA)	post-operative days	8/1495 (0.5%)
	Enoxaparin (LMWH)		18/1516 (1.2%)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	30 days	0/198 (0%)
	Enoxaparin (LMWH)		11/194 (5.7%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	0/211 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/224 (0%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	0/67 (0%)
	Heparin (UFH)		0/69 (0%)
Eriksson 1997B 9358126	Enoxaparin (NA)	Post-operative days	1/365 (0.3%)
	Desirudin (NA)		2/349 (0.6%)
	Enoxaparin (NA)		0/351 (0%)
	Desirudin (NA)		8/1032 (0.8%)
	Enoxaparin (NA)		2/1026 (0.2%)
	Desirudin (DTI)		20/1028 (1.9%)
	Enoxaparin (LMWH)		20/1023 (2.0%)
	Desirudin (NA)		5/275 (1.8%)
	Enoxaparin (NA)		1/294 (0.3%)
Eriksson 2005 15634273 THA	Dabigatran 150 mg (DTI)	post-operative years	10/266 (3.8%)
	Dabigatran 300 mg (NA)		12/258 (4.7%)

Study	Arm	Timepoint	n/N (%)
	Enoxaprin (LMWH)		6/270 (2.2%)
	Dabigatran 50 mg (NA)		0/265 (0%)
	Dabigatran 225 mg (NA)		12/270 (4.4%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	15/1163 (1.3%)
	Dabigatran 220 mg (DTI)		23/1146 (2.0%)
	Enoxaparin (LMWH)		18/1154 (1.6%)
Eriksson 2010 20088935	Darexaban 60 mg qD (NA)	9 days	1/163 (0.6%)
	Darexaban 5 mg (NA)		0/158 (0%)
	Enoxaparin 40 mg (NA)		1/166 (0.6%)
	Darexaban 120 mg (NA)		0/156 (0%)
	Darexaban 30 mg qD (NA)		0/156 (0%)
	Darexaban 10 mg (NA)		0/161 (0%)
	Darexaban 60 mg qD (FXaI)	6 weeks	1/163 (0.6%)
	Darexaban 5 mg (NA)		0/158 (0%)
	Enoxaparin 40 mg (LMWH)		1/166 (0.6%)
	Darexaban 120 mg (NA)		0/156 (0%)
	Darexaban 30 mg qD (NA)		0/156 (0%)
	Darexaban 10 mg (NA)		0/161 (0%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	14/1010 (1.4%)
	Enoxaparin (LMWH)		9/1003 (0.9%)
Francis 1997 9314399	Dalteparin (LMWH)	Post-operative days	6/271 (2.2%)
	Warfarin (VKA)		4/279 (1.4%)
Fuji 2008 18843459 THA	Placebo (Placebo)	post-operative years	0/101 (0%)
	Enoxaparin 40 mg (LMWH)		2/102 (2.0%)
	Enoxaparin 20 mg (NA)		3/104 (2.9%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	1/85 (1.2%)
	Edoxaban 15 mg (NA)		0/89 (0%)
	Enoxaparin 20 mg BID (LMWH)		0/87 (0%)

Study	Arm	Timepoint	n/N (%)
Fuji 2014D 22952213 THA	Placebo (NA)	10-14 (during treatment period) days	0/163 (0%)
	Darexaban 15 mg BID (NA)		0/169 (0%)
	Darexaban 30 mg BID (NA)		0/174 (0%)
	Enoxaparin (NA)		0/103 (0%)
	Placebo (Placebo)	3-5 weeks after the last dose (till study ended) weeks	0/163 (0%)
	Darexaban 15 mg BID (NA)		0/169 (0%)
	Darexaban 30 mg BID (FXaI)		0/174 (0%)
	Enoxaparin (LMWH)		0/103 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	2/303 (0.7%)
	Enoxaparin (LMWH)		6/301 (2.0%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	Post-operative days	11/398 (2.8%)
	Warfarin (VKA)		6/397 (1.5%)
Hull 2000 10904464	Warfarin (VKA)	0-1 days	20/489 (4.1%)
	Dalteparin preoperative (NA)		33/496 (6.7%)
	Dalteparin postoperative (LMWH)		28/487 (5.7%)
	Warfarin (NA)	2-8 days	2/489 (0.4%)
	Dalteparin preoperative (NA)		11/496 (2.2%)
	Dalteparin postoperative (NA)		4/487 (0.8%)
Kim 1998 9549575	Control (undefined) (Placebo)	post-operative days	0/50 (0%)
	Aspirin (Antiplatelet)		0/50 (0%)
Lassen 1998 9669750	Dalteparin (NA)	35 days	1/141 (0.7%)
	Extended Dalteparin (NA)		0/140 (0%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	47/1140 (4.1%)
	Enoxaparin (LMWH)		32/1133 (2.8%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	22/2673 (0.8%)
	Enoxaparin (LMWH)		18/2659 (0.7%)
Lassen 2012 22429800 THA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3	4/1153 (0.3%)

Study	Arm	Timepoint	n/N (%)
		calendar days days	
	Enoxaparin (NA)		14/1155 (1.2%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	19/332 (5.7%)
	Enoxaparin (LMWH)		11/333 (3.3%)
Menzin 1994 8173149	Enoxaparin 40 mg (LMWH)	Post-operative days	3/202 (1.5%)
	Enoxaparin 30 mg (NA)		8/192 (4.2%)
	Heparin (UFH)		13/209 (6.2%)
Paiement 1987 3572408	IPC (Mechanical)	Post-operative days	0/66 (0%)
	Warfarin (VKA)		0/72 (0%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	0/112 (0%)
	Enoxaparin (LMWH)		2/124 (1.6%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	0/90 (0%)
	Enoxaparin to discharge (NA)		0/89 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	2/251 (0.8%)
	Enoxaparin (NA)		4/248 (1.6%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	60 days	1/184 (0.5%)
	Warfarin until hospital discharge (NA)		0/176 (0%)
Raskob 2010 20589317	Edoxaban 90 mg (NA)	10 days	2/171 (1.2%)
	Edoxaban 60 mg (NA)		1/185 (0.5%)
	Edoxaban 30 mg (FXaI)		1/170 (0.6%)
	Edoxaban 15 mg (NA)		1/192 (0.5%)
	Dalteparin 5000 IU (LMWH)		0/172 (0%)
Sakai 2016 26735531	Edoxaban	28 days	3/62 (4.8)
	Edoxaban + foot pump		3/58 (5.2)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	1/75 (1.3%)
	Enoxaparin (LMWH)		1/78 (1.3%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		2/50 (4.0%)

Study	Arm	Timepoint	n/N (%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	2/50 (4.0%)
	Enoxaparin (LMWH)		1/50 (2.0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	20/1128 (1.8%)
	Enoxaparin (LMWH)		11/1129 (1.0%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	5/208 (2.4%)
	TB-402 25 mg (NA)		4/207 (1.9%)
	Rivaroxaban 10 mg (FXaI)		0/207 (0%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/85 (0%)
	Fondaparinux (FXaI)		0/85 (0%)
	Enoxaparin (LMWH)		0/85 (0%)
Major Bleeding: Complicated wound bleeding requiring Transfusion >=6 units of packed RBC			
Kim 2016 26790579a	Placebo	2 days after treatment	3/185 (1.6)
	Rivaroxaban		4/184 (2.2)
	Enoxaparin		4/184 (2.2)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	3/166 (1.8)
	Enoxaparin		3/167 (1.8)
Major Bleeding: Complicated wound bleeding requiring Prolonged hospitalisation >= 1 week			
Kim 2016 26790579a	Placebo	2 days after treatment	4/185 (2.2)
	Rivaroxaban		6/184 (3.3)
	Enoxaparin		5/184 (2.7)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	6/166 (3.6)
	Enoxaparin		5/167 (3)
Major Bleeding: Complicated wound bleeding requiring Medical intervention to manage hypotension			
Kim 2016 26790579a	Placebo	2 days after treatment	1/185 (0.5)
	Rivaroxaban		1/184 (0.5)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin		1/184 (0.5)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	1/166 (0.6)
	Enoxaparin		1/167 (0.6)
Bleeding, Surgical site/joint			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	0/133 (0)
	Dabigatran Etexilate 150 mg		0/126 (0)
	Dabigatran Etexilate 220 mg		1/129 (0.8)
Anderson 2013 23732713	Dalteparin (NA)	~100 days	5/400 (1.3%)
	Dalteparin then Aspirin (NA)		4/385 (1.0%)
Borgen 2012 22476844	Dalteparin (postop) (NA)	~8 days	4/40 (10%)
	Dalteparin (preop) (NA)		3/40 (7.5%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	7/247 (2.8%)
	Certoparin 5000 IU (NA)		4/232 (1.7%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative days	1/203 (0.5%)
	Enoxaparin 30 mg (NA)		6/195 (3.1%)
	Heparin (UFH)		7/209 (3.3%)
Colwell 1999 10428124	Warfarin (VKA)	post-operative days	5/1495 (0.3%)
	Enoxaparin (LMWH)		14/1516 (0.9%)
	Warfarin (VKA)		45/1495 (3.0%)
	Enoxaparin (LMWH)		62/1516 (4.1%)
Eriksson 1996 8596376	Desirudin (DTI)	Post-operative days	8/277 (2.9%)
	Heparin (UFH)		7/277 (2.5%)
Eriksson 1997B 9358126	Desirudin (DTI)	Post-operative days	336/1042 (32%)
	Enoxaparin (LMWH)		341/1036 (33%)
Francis 1997 9314399	Dalteparin (LMWH)	Post-operative days	12/271 (4.4%)
	Warfarin (VKA)		3/279 (1.1%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	2/303 (0.7%)
	Enoxaparin (LMWH)		1/301 (0.3%)

Study	Arm	Timepoint	n/N (%)
Hull 2000 10904464	Warfarin (NA)	0-1 days	0/489 (0%)
	Dalteparin preoperative (NA)		0/496 (0%)
	Dalteparin postoperative (NA)		1/487 (0.2%)
	Warfarin (NA)	2-8 days	0/489 (0%)
	Dalteparin preoperative (NA)		0/496 (0%)
	Dalteparin postoperative (NA)		2/487 (0.4%)
	Warfarin (VKA)	0-1 days	17/489 (3.5%)
	Dalteparin preoperative (NA)		32/496 (6.5%)
	Dalteparin postoperative (LMWH)		27/487 (5.5%)
	Warfarin (NA)	2-8 days	2/489 (0.4%)
	Dalteparin preoperative (NA)		9/496 (1.8%)
	Dalteparin postoperative (NA)		3/487 (0.6%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	40/1140 (3.5%)
	Enoxaparin (LMWH)		29/1133 (2.6%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	2/2673 (0.1%)
	Enoxaparin (LMWH)		4/2659 (0.2%)
	Apixaban (FXaI)		18/2673 (0.7%)
	Enoxaparin (LMWH)		16/2659 (0.6%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	2/251 (0.8%)
	Enoxaparin (NA)		4/248 (1.6%)
Sakai 2016 26735531	Edoxaban	28 days	2/62 (3.2)
	Edoxaban + foot pump		2/58 (3.4)
Senaran 2006 16333632	Heparin (UFH)	42 days	4/50 (8.0%)
	Enoxaparin (LMWH)		3/50 (6.0%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	24/208 (12%)
	TB-402 25 mg (NA)		19/207 (9.2%)
	Rivaroxaban 10 mg (FXaI)		9/207 (4.3%)
DVT, Proximal			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	2/115 (1.7)

Study	Arm	Timepoint	n/N (%)
	Dabigatran Etexilate 150 mg		2/113 (1.8)
	Dabigatran Etexilate 220 mg		0/102 (0)
Anderson 2013 23732713	Dalteparin (NA)	~100 days	2/398 (0.5%)
	Dalteparin then Aspirin (NA)		1/380 (0.3%)
Avikainen 1995 7645915	Heparin (UFH)	Post-operative days	4/84 (4.8%)
	Enoxaparin (LMWH)		1/83 (1.2%)
Bailey 1991 1774568	IPC (Mechanical)	Post-operative days	2/50 (4.0%)
	Warfarin (VKA)		0/45 (0%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	9/193 (4.7%)
	Certoparin 5000 IU (NA)		9/205 (4.4%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative days	8/203 (3.9%)
	Enoxaparin 30 mg (NA)		4/194 (2.1%)
	Heparin (UFH)		10/207 (4.8%)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	10 days	3/196 (1.5%)
	Enoxaparin (LMWH)		2/190 (1.1%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	27/211 (13%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		6/224 (2.7%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	35 days	10/114 (8.8%)
	Dalteparin 7 days (NA)		14/104 (13%)
Dechavanne 1989 2537787	Dalteparin 2500 U q12h (NA)	Post-operative days	1/41 (2.4%)
	Dalteparin 5000 U qD (LMWH)		1/41 (2.4%)
	Heparin (UFH)		3/40 (7.5%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/65 (0%)
	Enoxaparin (LMWH)		0/59 (0%)
Eriksson 1996 8596376	Desirudin (DTI)	Post-operative days	6/195 (3.1%)
	Heparin (UFH)		43/219 (20%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	3/174 (1.7%)
	Heparin (UFH)		16/177 (9.0%)

Study	Arm	Timepoint	n/N (%)
Eriksson 1997B 9358126	Desirudin (DTI)	Post-operative days	36/802 (4.5%)
	Enoxaparin (LMWH)		59/785 (7.5%)
Eriksson 2005 15634273 THA	Dabigatran 150 mg (DTI)	post-operative years	8/201 (4.0%)
	Dabigatran 300 mg (NA)		3/191 (1.6%)
	Enoxaprin (LMWH)		11/208 (5.3%)
	Dabigatran 50 mg (NA)		12/208 (5.8%)
	Dabigatran 225 mg (NA)		4/204 (2.0%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	2/120 (1.7%)
	Darexaban 5 mg (NA)		6/117 (5.1%)
	Enoxaparin 40 mg (LMWH)		5/127 (3.9%)
	Darexaban 120 mg (NA)		1/110 (0.9%)
	Darexaban 30 mg qD (NA)		5/114 (4.4%)
	Darexaban 10 mg (NA)		7/120 (5.8%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	17/804 (2.1%)
	Enoxaparin (LMWH)		31/792 (3.9%)
Fordyce 1992 1732264	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative days	2/39 (5.1%)
	Control (Placebo)		5/40 (13%)
Francis 1992 1583760	IPC (Mechanical)	Post-operative days	12/98 (12%)
	Warfarin (VKA)		3/103 (2.9%)
Francis 1997 9314399	Dalteparin (LMWH)	Post-operative days	10/192 (5.2%)
	Warfarin (VKA)		16/190 (8.4%)
Fuji 2008 18843459 THA	Placebo (Placebo)	post-operative years	9/86 (10%)
	Enoxaparin 40 mg (LMWH)		6/80 (7.5%)
	Enoxaparin 20 mg (NA)		3/90 (3.3%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/72 (0%)
	Edoxaban 15 mg (NA)		0/78 (0%)
	Enoxaparin 20 mg BID (LMWH)		0/74 (0%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment	5/137 (3.6%)

Study	Arm	Timepoint	n/N (%)
		period) days	
	Darexaban 15 mg BID (NA)		1/144 (0.7%)
	Darexaban 30 mg BID (FXaI)		0/174 (0%)
	Enoxaparin (LMWH)		0/103 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	1/255 (0.4%)
	Enoxaparin (LMWH)		2/248 (0.8%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	Post-operative days	16/332 (4.8%)
	Warfarin (VKA)		13/340 (3.8%)
Hull 2000 10904464	Warfarin (VKA)	post-operative days	11/363 (3.0%)
	Dalteparin preoperative (NA)		3/354 (0.8%)
	Dalteparin postoperative (LMWH)		3/358 (0.8%)
Kalodiki 1996 8803642	Placebo (Placebo)	Post-operative days	8/14 (57%)
	GCS+ Enoxaparin (LMWH_Mechanical)		4/32 (13%)
	Enoxaparin (LMWH)		9/32 (28%)
Lassen 1991 1848385	Placebo (Placebo)	Post-operative days	35/97 (36%)
	Tinzaparin (LMWH)		24/93 (26%)
Lassen 1998 9669750	Dalteparin (NA)	35 days	5/101 (5.0%)
	Extended Dalteparin (NA)		1/111 (0.9%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	6/922 (0.7%)
	Enoxaparin (LMWH)		23/927 (2.5%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	7/2196 (0.3%)
	Enoxaparin (LMWH)		20/2190 (0.9%)
Lassen 2012 22429800 THA	Semuloparin (NA)	7-11 days	13/1002 (1.3%)
	Enoxaparin (NA)		15/1011 (1.5%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	17/263 (6.5%)
	Enoxaparin (LMWH)		14/258 (5.4%)
Lieberman 1994 8126039	Aspirin (Antiplatelet)	Post-operative days	7/124 (5.6%)
	Aspirin+IPC (Antiplatelet_Mechanical)		0/124 (0%)
Lotke 1996 8595765 THA	Aspirin (Antiplatelet)	Post-operative days	3/62 (4.8%)

Study	Arm	Timepoint	n/N (%)
	Warfarin (VKA)		10/71 (14%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	28/131 (21%)
	Enoxaparin 30 days (NA)		8/131 (6.1%)
Paiement 1987 3572408	IPC (Mechanical)	Post-operative days	10/66 (15%)
	Warfarin (VKA)		5/72 (6.9%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	20/108 (19%)
	Enoxaparin (LMWH)		9/120 (7.5%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	5/85 (5.9%)
	Enoxaparin to discharge (NA)		7/88 (8.0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	21/221 (10%)
	Enoxaparin (NA)		23/219 (11%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	60 days	1/184 (0.5%)
	Warfarin until hospital discharge (NA)		3/176 (1.7%)
Raskob 2010 20589317	Edoxaban 90 mg (NA)	7-10 days	2/151 (1.3%)
	Edoxaban 60 mg (NA)		2/158 (1.3%)
	Edoxaban 30 mg (FXaI)		5/151 (3.3%)
	Edoxaban 15 mg (NA)		11/170 (6.5%)
	Dalteparin 5000 IU (LMWH)		20/144 (14%)
Ryan 2002 12429761	IPC (Venaflow) (NA)	post-operative days	4/50 (8.0%)
	GCS (T.E.D.) (NA)		11/50 (22%)
Sakai 2016 26735531	Edoxaban	28 days	0/62 (0)
	Edoxaban + foot pump		0/58 (0)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	12/75 (16%)
	Enoxaparin (LMWH)		2/78 (2.6%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	5/47 (11%)
	Enoxaparin (LMWH)		4/52 (7.7%)
Silbersack 2004 15330019 THA	Enoxaparin + GCS (Comprinet Pro) (NA)	6-12th post-operative days	1/28 (3.6%)
	Enoxaparin + IPC (Venaflow) (NA)		0/33 (0%)

Study	Arm	Timepoint	n/N (%)
Stannard 1996 8640382	VFP (PlexiPulse) (NA)	Post-operative days	0/25 (0%)
	VFP (PlexiPulse)+ Heparin then Aspirin (NA)		0/25 (0%)
	Heparin then Aspirin (NA)		5/25 (20%)
Stone 1996 9049766	IPC (Mechanical)	Post-operative days	1/25 (4.0%)
	Enoxaparin (LMWH)		1/25 (4.0%)
Tørholm 1991 1670445	Placebo (Placebo)	Post-operative days	4/54 (7.4%)
	Dalteparin (LMWH)		0/58 (0%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	9/39 (23%)
	Enoxaparin (LMWH)		2/37 (5.4%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	14/816 (1.7%)
	Enoxaparin (LMWH)		10/830 (1.2%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	4/193 (2.1%)
	TB-402 25 mg (NA)		1/187 (0.5%)
	Rivaroxaban 10 mg (FXaI)		1/191 (0.5%)
Warwick 1995 7559695	Control (Placebo)	Post-operative days	14/78 (18%)
	Enoxaparin (LMWH)		12/78 (15%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	17/136 (13%)
	Enoxaparin (LMWH)		12/138 (8.7%)
Woolson 1991 2013589	IPC+ Aspirin (Antiplatelet_Mechanical)	Post-operative days	7/72 (10%)
	IPC (Mechanical)		9/76 (12%)
	IPC+ wafarin (VKA_Mechanical)		6/69 (8.7%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/83 (0%)
	Fondaparinux (FXaI)		1/84 (1.2%)
	Enoxaparin (LMWH)		0/83 (0%)
Zhang 2013 EMBASE 2014592535	Rivaroxaban (FXaI)	6 months	0/53 (0%)
	LMWH (LMWH)		7/53 (13%)
DVT, Symptomatic			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	1/133 (0.8)
	Dabigatran Etexilate 150 mg		2/126 (1.6)

Study	Arm	Timepoint	n/N (%)
	Dabigatran Etexilate 220 mg		1/129 (0.8)
Andersen 1997 9690480	Dalteparin 35 days (NA)	35 days	1/20 (5.0%)
	Dalteparin 5-7 days (NA)		1/21 (4.8%)
Anderson 2013 23732713	Dalteparin (NA)	~100 days	3/398 (0.8%)
	Dalteparin then Aspirin (NA)		1/380 (0.3%)
Avikainen 1995 7645915	Heparin (UFH)	Post-operative days	4/84 (4.8%)
	Enoxaparin (LMWH)		1/83 (1.2%)
Borgen 2012 22476844	Dalteparin (postop) (NA)	~8 days	0/40 (0%)
	Dalteparin (preop) (NA)		0/40 (0%)
Colwell 1999 10428124	Warfarin (VKA)	90 days	47/1495 (3.1%)
	Enoxaparin (LMWH)		49/1516 (3.2%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	35 days	8/114 (7.0%)
	Dalteparin 7 days (NA)		4/104 (3.8%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	2/63 (3.2%)
	Heparin (UFH)		2/59 (3.4%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	9/1156 (0.8%)
	Dabigatran 220mg (DTI)		6/1137 (0.5%)
	Enoxaparin (LMWH)		1/1142 (0.1%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	1/120 (0.8%)
	Darexaban 5 mg (NA)		1/117 (0.9%)
	Enoxaparin 40 mg (LMWH)		0/127 (0%)
	Darexaban 120 mg (NA)		1/110 (0.9%)
	Darexaban 30 mg qD (NA)		0/114 (0%)
	Darexaban 10 mg (NA)		1/120 (0.8%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	0/1001 (0%)
	Enoxaparin (LMWH)		4/992 (0.4%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/72 (0%)
	Edoxaban 15 mg (NA)		0/78 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin 20 mg BID (LMWH)		0/74 (0%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	0/163 (0%)
	Darexaban 15 mg BID (NA)		0/169 (0%)
	Darexaban 30 mg BID (FXaI)		0/174 (0%)
	Enoxaparin (LMWH)		0/103 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	0/255 (0%)
	Enoxaparin (LMWH)		0/248 (0%)
Hull 2000 10904464	Warfarin (VKA)	post-operative days	15/338 (4.4%)
	Dalteparin preoperative (NA)		5/337 (1.5%)
	Dalteparin postoperative (LMWH)		10/336 (3.0%)
Kim 2016 26790579a	Placebo	2 days after treatment	4/185 (2.2)
	Rivaroxaban		3/184 (1.6)
	Enoxaparin		4/184 (2.2)
Kim 2016 26790579a	Placebo	4 weeks post-treatment	4/185 (2.2)
	Rivaroxaban		3/184 (1.6)
	Enoxaparin		4/184 (2.2)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	3/166 (1.8)
	Enoxaparin		3/167 (1.8)
Kim 2016 26790579b	Rivaroxaban	4 weeks post-treatment	3/166 (1.8)
	Enoxaparin		3/167 (1.8)
Lassen 1991 1848385	Placebo (Placebo)	Post-operative days	0/97 (0%)
	Tinzaparin (LMWH)		0/93 (0%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	3/1129 (0.3%)
	Enoxaparin (LMWH)		1/1123 (0.1%)
Lassen 2010A 21175312	Apixaban (NA)	On treatment, ~34 days	1/2708 (0.04%)
	Enoxaparin (NA)		5/2699 (0.2%)
	Apixaban (FXaI)	Post-treatment, ~94 days	1/2708 (0.04%)
	Enoxaparin (LMWH)		8/2699 (0.3%)

Study	Arm	Timepoint	n/N (%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	8/131 (6.1%)
	Enoxaparin 30 days (NA)		2/131 (1.5%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	2/221 (0.9%)
	Enoxaparin (NA)		3/219 (1.4%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	60 days	2/184 (1.1%)
	Warfarin until hospital discharge (NA)		3/176 (1.7%)
Ryan 2002 12429761	IPC (Venaflow) (NA)	post-operative days	0/50 (0%)
	GCS (T.E.D.) (NA)		0/50 (0%)
Sakai 2016 26735531	Edoxaban	28 days	1/62 (1.6)
	Edoxaban + foot pump		3/58 (5.2)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	1/75 (1.3%)
	Enoxaparin (LMWH)		1/78 (1.3%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	3/47 (6.4%)
	Enoxaparin (LMWH)		3/52 (5.8%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		2/50 (4.0%)
Stannard 1996 8640382	VFP (PlexiPulse) (NA)	Post-operative days	0/25 (0%)
	VFP (PlexiPulse)+ Heparin then Aspirin (NA)		0/25 (0%)
	Heparin then Aspirin (NA)		3/25 (12%)
Stone 1996 9049766	IPC (Mechanical)	Post-operative days	0/25 (0%)
	Enoxaparin (LMWH)		0/25 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	5/1126 (0.4%)
	Enoxaparin (LMWH)		0/1128 (0%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	0/193 (0%)
	TB-402 25 mg (NA)		0/187 (0%)
	Rivaroxaban 10 mg (FXaI)		0/191 (0%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	0/136 (0%)
	Enoxaparin (LMWH)		1/138 (0.7%)

Study	Arm	Timepoint	n/N (%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/83 (0%)
	Fondaparinux (FXaI)		1/84 (1.2%)
	Enoxaparin (LMWH)		0/83 (0%)
DVT, Total			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	42/106 (39.6)
	Dabigatran Etexilate 150 mg		34/104 (32.7)
	Dabigatran Etexilate 220 mg		23/96 (24)
Alfaro 1986 3535158	Aspirin 125 mg (Antiplatelet)	Post-operative	1/30 (3.3%)
	Control (Placebo)		9/30 (30%)
	Aspirin 500 mg (NA)		1/30 (3.3%)
Andersen 1997 9690480	Dalteparin 35 days (NA)	35 days	2/20 (10%)
	Dalteparin 5-7 days (NA)		3/21 (14%)
Avikainen 1995 7645915	Heparin (UFH)	Post-operative	4/84 (4.8%)
	Enoxaparin (LMWH)		1/83 (1.2%)
Bailey 1991 1774568	IPC (Mechanical)	Post-operative	3/50 (6.0%)
	Warfarin (VKA)		12/45 (27%)
Barre 1987 2834500	Dalteparin (LMWH)	Post-operative	7/40 (18%)
	Heparin (UFH)		4/40 (10%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	28/193 (15%)
	Certoparin 5000 IU (NA)		35/205 (17%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative	30/203 (15%)
	Enoxaparin 30 mg (NA)		9/194 (4.6%)
	Heparin (UFH)		24/207 (12%)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	10 days	8/196 (4.1%)
	Enoxaparin (LMWH)		8/190 (4.2%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	49/211 (23%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		18/224 (8.0%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	7-35 days	11/93 (12%)

Study	Arm	Timepoint	n/N (%)
	Dalteparin 7 days (NA)		23/89 (26%)
Dechavanne 1989 2537787	Dalteparin 2500 U q12h (NA)	Post-operative	2/41 (4.9%)
	Dalteparin 5000 U qD (LMWH)		3/41 (7.3%)
	Heparin (UFH)		4/40 (10%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	Post-operative	1/65 (1.5%)
	Enoxaparin (LMWH)		2/59 (3.4%)
Eisele 2007 17473143 THR	Certoparin + IPC	discharge	0/191 (0)
	Certoparin		6/115 (5.2)
Eisele 2007 17473143 TKR	Certoparin + IPC	discharge	3/79 (3.8)
	Certoparin		4/54 (7.4)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative	19/63 (30%)
	Heparin (UFH)		25/59 (42%)
Eriksson 1996 8596376	Desirudin (DTI)	Post-operative	37/202 (18%)
	Heparin (UFH)		77/229 (34%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	13/180 (7.2%)
	Heparin (UFH)		42/180 (23%)
Eriksson 1997B 9358126	Desirudin (DTI)	Post-operative	142/773 (18%)
	Enoxaparin (LMWH)		196/768 (26%)
Eriksson 2005 15634273 THA	Dabigatran 150 mg (DTI)	post-operative	26/201 (13%)
	Dabigatran 300 mg (NA)		25/191 (13%)
	Enoxaprin (LMWH)		31/208 (15%)
	Dabigatran 50 mg (NA)		49/208 (24%)
	Dabigatran 225 mg (NA)		17/204 (8.3%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	16/120 (13%)
	Darexaban 5 mg (NA)		32/117 (27%)
	Enoxaparin 40 mg (LMWH)		24/127 (19%)
	Darexaban 120 mg (NA)		15/110 (14%)
	Darexaban 30 mg qD (NA)		22/114 (19%)
	Darexaban 10 mg (NA)		38/120 (32%)

Study	Arm	Timepoint	n/N (%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	60/791 (7.6%)
	Enoxaparin (LMWH)		67/783 (8.6%)
Fordyce 1992 1732264	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative	4/39 (10%)
	Control (Placebo)		16/40 (40%)
Francis 1992 1583760	IPC (Mechanical)	Post-operative	26/98 (27%)
	Warfarin (VKA)		32/103 (31%)
Francis 1997 9314399	Dalteparin (LMWH)	Post-operative	28/192 (15%)
	Warfarin (VKA)		49/190 (26%)
Fuji 2008 18843459 THA	Placebo (Placebo)	Post-operative	36/86 (42%)
	Enoxaparin 40 mg (LMWH)		27/80 (34%)
	Enoxaparin 20 mg (NA)		18/90 (20%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	2/72 (2.8%)
	Edoxaban 15 mg (NA)		3/78 (3.8%)
	Enoxaparin 20 mg BID (LMWH)		3/74 (4.1%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	22/129 (17%)
	Darexaban 15 mg BID (NA)		4/136 (2.9%)
	Darexaban 30 mg BID (FXaI)		6/133 (4.5%)
	Enoxaparin (LMWH)		2/82 (2.4%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	6/255 (2.4%)
	Enoxaparin (LMWH)		17/248 (6.9%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	Post-operative	69/332 (21%)
	Warfarin (VKA)		79/340 (23%)
Hull 2000 10904464	Warfarin (VKA)	post-operative days	81/338 (24%)
	Dalteparin preoperative (NA)		36/337 (11%)
	Dalteparin postoperative (LMWH)		44/336 (13%)
Kalodiki 1996 8803642	Placebo (Placebo)	Post-operative	13/14 (93%)
	GCS+ Enoxaparin (LMWH_Mechanical)		8/32 (25%)
	Enoxaparin (LMWH)		12/32 (38%)

Study	Arm	Timepoint	n/N (%)
Kim 1998 9549575	Control (undefined) (Placebo)	post-operative days	10/50 (20%)
	Aspirin (Antiplatelet)		6/50 (12%)
Kim 2016 26790579a	Placebo	2 days after treatment	12/185 (6.5)
	Rivaroxaban		10/184 (5.4)
	Enoxaparin		11/184 (6)
Kim 2016 26790579a	Placebo	4 weeks post-treatment	12/185 (6.5)
	Rivaroxaban		10/184 (5.4)
	Enoxaparin		11/184 (6)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	14/166 (8.4)
	Enoxaparin		12/167 (7.2)
Kim 2016 26790579b	Rivaroxaban	4 weeks post-treatment	14/166 (8.4)
	Enoxaparin		12/167 (7.2)
Lassen 1991 1848385	Placebo (Placebo)	Post-operative days	44/97 (45%)
	Tinzaparin (LMWH)		29/93 (31%)
Lassen 1998 9669750	Dalteparin (NA)	35 days	12/102 (12%)
	Extended Dalteparin (NA)		5/113 (4.4%)
Lassen 2002 12049858	Fondaparinux (FXaI)	11 days	36/908 (4.0%)
Lass	Enoxaparin (LMWH)		83/918 (9.0%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	22/1944 (1.1%)
	Enoxaparin (LMWH)		68/1911 (3.6%)
Lassen 2012 22429800 THA	Semuloparin (NA)	7-11 days	57/915 (6.2%)
	Enoxaparin (NA)		102/931 (11%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	61/263 (23%)
	Enoxaparin (LMWH)		50/258 (19%)
Lotke 1996 8595765 THA	Aspirin (Antiplatelet)	Post-operative	18/62 (29%)
	Warfarin (VKA)		26/71 (37%)
Lou 2010 20646562	LMWH (LMWH)	7 days	3/38 (7.9%)
	Control (Placebo)		15/35 (43%)
Menzin 1994 8173149	Enoxaparin 40 mg (LMWH)	Post-operative	30/202 (15%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin 30 mg (NA)		9/192 (4.7%)
	Heparin (UFH)		24/209 (11%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	43/131 (33%)
	Enoxaparin 30 days (NA)		21/131 (16%)
Paiement 1987 3572408	IPC (Mechanical)	Post-operative	11/66 (17%)
	Warfarin (VKA)		12/72 (17%)
Planes 1988 2853459	Heparin (UFH)	Post-operative	27/108 (25%)
	Enoxaparin (LMWH)		15/120 (13%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	6/85 (7.1%)
	Enoxaparin to discharge (NA)		17/88 (19%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative	48/221 (22%)
	Enoxaparin (NA)		44/219 (20%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	60 days	3/184 (1.6%)
	Warfarin until hospital discharge (NA)		8/176 (4.5%)
Rader 1998 9526211 THA	Heparin + Heparin (NA)	Post-operative	1/56 (1.8%)
	Heparin + Enoxaparin (NA)		2/70 (2.9%)
Sakai 2016 26735531	Edoxaban	28 days	11/62 (17.7)
	Edoxaban + foot pump		18/58 (31)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	28/75 (37%)
	Enoxaparin (LMWH)		11/78 (14%)
Santori 1994 8027144	VFP (Mechanical)	42 days	9/67 (13%)
	Heparin (UFH)		23/65 (35%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative	5/47 (11%)
	Enoxaparin (LMWH)		5/52 (10%)
Senaran 2006 16333632	Heparin (UFH)	discharge days	2/50 (4.0%)
	Enoxaparin (LMWH)		0/50 (0%)
Silbersack 2004 15330019 THA	Enoxaparin + GCS (Comprinet Pro) (NA)	6-12th post-operative days	4/28 (14%)
	Enoxaparin + IPC (Venaflow) (NA)		0/33 (0%)

Study	Arm	Timepoint	n/N (%)
Sørensen 1990 1966794	Placebo (Placebo)	Post-operative	16/33 (48%)
	Tinzaparin (LMWH)		17/31 (55%)
Stannard 1996 8640382	VFP (PlexiPulse) (NA)	Post-operative	0/25 (0%)
	VFP (PlexiPulse)+ Heparin then Aspirin (NA)		0/25 (0%)
	Heparin then Aspirin (NA)		5/25 (20%)
Stone 1996 9049766	IPC (Mechanical)	Post-operative	1/25 (4.0%)
	Enoxaparin (LMWH)		1/25 (4.0%)
Tørholm 1991 1670445	Placebo (Placebo)	Post-operative	16/54 (30%)
	Dalteparin (LMWH)		8/58 (14%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative	20/39 (51%)
	Enoxaparin (LMWH)		4/37 (11%)
Turpie 2002 12049860	Fondaparinux (FXaI)	11 days	44/784 (5.6%)
	Enoxaparin (LMWH)		65/796 (8.2%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	10/193 (5.2%)
	TB-402 25 mg (NA)		10/187 (5.3%)
	Rivaroxaban 10 mg (FXaI)		9/191 (4.7%)
Warwick 1995 7559695	Control (Placebo)	Post-operative	33/78 (42%)
	Enoxaparin (LMWH)		22/78 (28%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	Post-operative	24/136 (18%)
	Enoxaparin (LMWH)		18/138 (13%)
Welin-Berger 1982 6184938	Heparin (UFH)	Post-operative	8/20 (40%)
	Control (Placebo)		5/20 (25%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	6/83 (7.2%)
	Fondaparinux (FXaI)		6/84 (7.1%)
	Enoxaparin (LMWH)		5/83 (6.0%)
Zhang 2013 EMBASE 2014592535	Rivaroxaban (FXaI)	6 months	0/53 (0%)
	LMWH (LMWH)		7/53 (13%)
Zhang 2014 24767296	Rivaroxaban 35 days (NA)	35 days	0/20 (0%)
	Rivaroxaban 7 days (NA)		0/20 (0%)

Study	Arm	Timepoint	n/N (%)
Zhirova 2014 25831700	enoxaparin + rivaroxaban (NA)	in hospital N/A	5/40 (13%)
	enoxaparin + dabigatran (NA)		3/42 (7.1%)
	enoxaparin (NA)		6/39 (15%)
Heparin-induced thrombocytopenia			
Colwell 1994 8288662	Enoxaparin 40 mg (NA)	Post-operative days	0/203 (0%)
	Enoxaparin 30 mg (NA)		0/195 (0%)
	Heparin (NA)		1/209 (0.5%)
Colwell 1999 10428124	Warfarin (NA)	post-operative days	0/1495 (0%)
	Enoxaparin (NA)		0/1516 (0%)
Levine 1991 1848054	Heparin (NA)	Post-operative days	9/332 (2.7%)
	Enoxaparin (NA)		0/333 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	0/251 (0%)
	Enoxaparin (NA)		1/248 (0.4%)
Senaran 2006 16333632	Heparin (NA)	42 days	0/50 (0%)
	Enoxaparin (NA)		0/50 (0%)
Infection, Joint			
Kim 2016 26790579a	Placebo	2 days after treatment	0/184 (0)
	Rivaroxaban		0/184 (0)
	Enoxaparin		0/184 (0)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	0/166 (0)
	Enoxaparin		0/167 (0)
Infection, Wound			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	0/133 (0)
	Dabigatran Etexilate 150 mg		1/126 (0.8)
	Dabigatran Etexilate 220 mg		0/129 (0)
Anderson 2013 23732713	Dalteparin (NA)	~100 days	10/400 (2.5%)
	Dalteparin then Aspirin (NA)		12/385 (3.1%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	0/252 (0%)
	Certoparin 5000 IU (NA)		0/248 (0%)

Study	Arm	Timepoint	n/N (%)
	Certoparin 3000 IU (NA)		2/252 (0.8%)
	Certoparin 5000 IU (NA)		5/248 (2.0%)
Kim 2016 26790579a	Placebo	2 days after treatment	0/185 (0)
	Rivaroxaban		0/184 (0)
	Enoxaparin		0/184 (0)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	0/166 (0)
	Enoxaparin		0/167 (0)
Major adverse event, other			
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	3 months	3/198 (1.5%)
	Enoxaparin (LMWH)		10/194 (5.2%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/85 (0%)
	Edoxaban 15 mg (NA)		0/89 (0%)
	Enoxaparin 20 mg BID (LMWH)		1/87 (1.1%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	4/163 (2.5%)
	Darexaban 15 mg BID (NA)		2/169 (1.2%)
	Darexaban 30 mg BID (FXaI)		1/174 (0.6%)
	Enoxaparin (LMWH)		3/103 (2.9%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	9/303 (3.0%)
	Enoxaparin (LMWH)		10/301 (3.3%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	184/2673 (6.9%)
	Enoxaparin (LMWH)		172/2659 (6.5%)
Lassen 2012 22429800 THA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days	32/1153 (2.8%)
	Enoxaparin (NA)		43/1155 (3.7%)
Raskob 2010 20589317	Edoxaban 90 mg (NA)	10 days	10/177 (5.6%)
	Edoxaban 60 mg (NA)		8/185 (4.3%)
	Edoxaban 30 mg (FXaI)		5/170 (2.9%)

Study	Arm	Timepoint	n/N (%)
	Edoxaban 15 mg (NA)		8/192 (4.2%)
	Dalteparin 5000 IU (LMWH)		3/172 (1.7%)
Mortality, 30 day or in-hospital (AE)			
2013 NCT00595426	Wafarin	nd	2/133 (1.5)
	Darexaban 60 mg QD		0/137 (0)
	Darexaban 30 mg BID		0/137 (0)
	Darexaban 60 mg BID		0/138 (0)
	Darexaban 120 mg QD		0/141 (0)
Bailey 1991 1774568	IPC (Mechanical)	Post-operative days	0/50 (0%)
	Warfarin (VKA)		0/45 (0%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative days	0/203 (0%)
	Enoxaparin 30 mg (NA)		1/195 (0.5%)
	Heparin (UFH)		2/209 (1.0%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	0/211 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/224 (0%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	35 days	1/134 (0.7%)
	Dalteparin 7 days (NA)		1/131 (0.8%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/65 (0%)
	Enoxaparin (LMWH)		0/59 (0%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	0/67 (0%)
	Heparin (UFH)		1/69 (1.4%)
Eriksson 1996 8596376	Desirudin (DTI)	42 days	0/202 (0%)
	Heparin (UFH)		1/229 (0.4%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	0/180 (0%)
	Heparin (UFH)		2/180 (1.1%)
Eriksson 1997B 9358126	Desirudin (DTI)	42 days	4/802 (0.5%)
	Enoxaparin (LMWH)		1/785 (0.1%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	3/1156 (0.3%)
	Dabigatran 220mg (DTI)		3/1137 (0.3%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		0/1142 (0%)
Eriksson 2011 21225098	Dabigatran 220 mg (DTI)	28-35 (during treatment period) days	0/1001 (0%)
	Enoxaparin (LMWH)		1/992 (0.1%)
Francis 1992 1583760	IPC (Mechanical)	Post-operative days	1/98 (1.0%)
	Warfarin (VKA)		1/103 (1.0%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	0/163 (0%)
	Darexaban 15 mg BID (NA)		0/169 (0%)
	Darexaban 30 mg BID (FXaI)		0/174 (0%)
	Enoxaparin (LMWH)		0/103 (0%)
Hull 2000 10904464	Warfarin (VKA)	Post-operative days	0/489 (0%)
	Dalteparin preoperative (NA)		2/496 (0.4%)
	Dalteparin postoperative (LMWH)		0/487 (0%)
Kim 2016 26790579a	Placebo	4 weeks post-treatment	0/185 (0)
	Rivaroxaban		0/184 (0)
	Enoxaparin		0/184 (0)
Kim 2016 26790579b	Rivaroxaban	4 weeks post-treatment	0/166 (0)
	Enoxaparin		0/167 (0)
Lassen 1991 1848385	Placebo (Placebo)	In-hospital days	1/97 (1.0%)
	Tinzaparin (LMWH)		1/93 (1.1%)
Lassen 2002 12049858	Fondaparinux (FXaI)	NR	2/1140 (0.2%)
	Enoxaparin (LMWH)		4/1133 (0.4%)
Lassen 2012 22429800 THA	Semuloparin (NA)	7-11 days	1/1150 (0.1%)
	Enoxaparin (NA)		2/1152 (0.2%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	0/332 (0%)
	Enoxaparin (LMWH)		0/333 (0%)
Lieberman 1994 8126039	Aspirin (Antiplatelet)	Post-operative days	0/118 (0%)
	Aspirin+IPC (Antiplatelet_Mechanical)		1/113 (0.9%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	0/108 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		0/120 (0%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	0/85 (0%)
	Enoxaparin to discharge (NA)		0/88 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	0/251 (0%)
	Enoxaparin (NA)		1/248 (0.4%)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	0/84 (0%)
	Enoxaparin (LMWH)		0/85 (0%)
Santori 1994 8027144	VFP (Mechanical)	42 days	0/67 (0%)
	Heparin (UFH)		1/65 (1.5%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	0/47 (0%)
	Enoxaparin (LMWH)		0/52 (0%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		0/50 (0%)
Sørensen 1990 1966794	Placebo (Placebo)	Post-operative days	1/33 (3.0%)
	Tinzaparin (LMWH)		1/31 (3.2%)
Stannard 1996 8640382	VFP (PlexiPulse) (NA)	Post-operative days	0/25 (0%)
	VFP (PlexiPulse)+ Heparin then Aspirin (NA)		0/25 (0%)
	Heparin then Aspirin (NA)		0/25 (0%)
Tørholm 1991 1670445	Placebo (Placebo)	Post-operative days	0/54 (0%)
	Dalteparin (LMWH)		1/58 (1.7%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	1/50 (2.0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	49 days	6/1128 (0.5%)
	Enoxaparin (LMWH)		3/1129 (0.3%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	0/208 (0%)
	TB-402 25 mg (NA)		1/207 (0.5%)
	Rivaroxaban 10 mg (FXaI)		1/207 (0.5%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	0/147 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		0/143 (0%)
PE, Fatal			
Anderson 2013 23732713	Dalteparin (NA)	~100 days	0/398 (0%)
	Dalteparin then Aspirin (NA)		0/380 (0%)
Barre 1987 2834500	Dalteparin (LMWH)	60 days	0/40 (0%)
	Heparin (UFH)		0/40 (0%)
Colwell 1994 8288662	Enoxaparin 40 mg (LMWH)	Post-operative days	0/203 (0%)
	Enoxaparin 30 mg (NA)		0/195 (0%)
	Heparin (UFH)		0/209 (0%)
Colwell 1999 10428124	Warfarin (VKA)	90 days	0/1495 (0%)
	Enoxaparin (LMWH)		1/1516 (0.1%)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	10 days	0/196 (0%)
	Enoxaparin (LMWH)		0/190 (0%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	0/211 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/224 (0%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	7-35 days	0/111 (0%)
	Dalteparin 7 days (NA)		1/106 (0.9%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	90 days	0/65 (0%)
	Enoxaparin (LMWH)		0/59 (0%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	0/65 (0%)
	Heparin (UFH)		0/62 (0%)
Eriksson 1996 8596376	Desirudin (DTI)	post-operative days	0/202 (0%)
	Heparin (UFH)		0/229 (0%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	0/180 (0%)
	Heparin (UFH)		0/180 (0%)
Eriksson 1997B 9358126	Desirudin (DTI)	Post-operative to 42 days	1/802 (0.1%)
	Enoxaparin (LMWH)		0/785 (0%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	1/1156 (0.1%)

Study	Arm	Timepoint	n/N (%)
	Dabigatran 220mg (DTI)		0/1137 (0%)
	Enoxaparin (LMWH)		0/1142 (0%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	0/120 (0%)
	Darexaban 5 mg (NA)		0/117 (0%)
	Enoxaparin 40 mg (LMWH)		0/127 (0%)
	Darexaban 120 mg (NA)		0/110 (0%)
	Darexaban 30 mg qD (NA)		0/114 (0%)
	Darexaban 10 mg (NA)		0/120 (0%)
Eriksson 2014 24136153	Enoxaparin 40 mg qD (LMWH)	12 days	0/314 (0%)
	Darexaban 30 mg qD (NA)		0/293 (0%)
	Darexaban 60 mg qD (FXaI)		0/274 (0%)
	Darexaban 30 mg BID (NA)		0/296 (0%)
	Darexaban 15 mg BID (NA)		0/269 (0%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/72 (0%)
	Edoxaban 15 mg (NA)		0/78 (0%)
	Enoxaparin 20 mg BID (LMWH)		0/74 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	0/255 (0%)
	Enoxaparin (LMWH)		0/248 (0%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	90 days	0/398 (0%)
	Warfarin (VKA)		0/397 (0%)
Hull 2000 10904464	Warfarin (VKA)	post-operative days	0/489 (0%)
	Dalteparin preoperative (NA)		0/496 (0%)
	Dalteparin postoperative (LMWH)		0/487 (0%)
Kim 2016 26790579a	Placebo	2 days after treatment	0/185 (0)
	Rivaroxaban		0/184 (0)
	Enoxaparin		0/184 (0)
Kim 2016 26790579a	Placebo	4 weeks post-treatment	0/185 (0)
	Rivaroxaban		0/184 (0)
	Enoxaparin		0/184 (0)

Study	Arm	Timepoint	n/N (%)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment	0/166 (0)
	Enoxaparin		0/167 (0)
Kim 2016 26790579b	Rivaroxaban	4 weeks post-treatment	0/166 (0)
	Enoxaparin		0/167 (0)
Lassen 1991 1848385	Placebo (Placebo)	Post-operative days	0/97 (0%)
	Tinzaparin (LMWH)		0/93 (0%)
Lassen 2002 12049858	Fondaparinux (FXaI)	49 days	0/1129 (0%)
	Enoxaparin (LMWH)		0/1123 (0%)
Lassen 2010A 21175312	Apixaban (NA)	~34 (on treatment) days	1/2708 (0.04%)
	Enoxaparin (NA)		0/2699 (0%)
	Apixaban (FXaI)	~94 (post-treatment) days	1/2708 (0.04%)
	Enoxaparin (LMWH)		0/2699 (0%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	0/332 (0%)
	Enoxaparin (LMWH)		0/333 (0%)
Lieberman 1994 8126039	Aspirin (Antiplatelet)	90 days	0/118 (0%)
	Aspirin+IPC (Antiplatelet_Mechanical)		0/113 (0%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	0/131 (0%)
	Enoxaparin 30 days (NA)		0/131 (0%)
Paiement 1987 3572408	IPC (Mechanical)	Post-operative days	0/66 (0%)
	Warfarin (VKA)		0/72 (0%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	0/108 (0%)
	Enoxaparin (LMWH)		0/120 (0%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	0/85 (0%)
	Enoxaparin to discharge (NA)		0/88 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	0/251 (0%)
	Enoxaparin (NA)		1/248 (0.4%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	28 days	0/184 (0%)
	Warfarin until hospital discharge (NA)		0/176 (0%)
Ryan 2002 12429761	IPC (Venaflow) (NA)	post-operative days	0/50 (0%)

Study	Arm	Timepoint	n/N (%)
	GCS (T.E.D.) (NA)		0/50 (0%)
Sakai 2016 26735531	Edoxaban	28 days	0/62 (0)
	Edoxaban + foot pump		0/58 (0)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	0/84 (0%)
	Enoxaparin (LMWH)		0/85 (0%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	0/47 (0%)
	Enoxaparin (LMWH)		0/52 (0%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	0/50 (0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	49 days	1/1126 (0.1%)
	Enoxaparin (LMWH)		2/1128 (0.2%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	0/193 (0%)
	TB-402 25 mg (NA)		0/187 (0%)
	Rivaroxaban 10 mg (FXaI)		0/191 (0%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	0/136 (0%)
	Enoxaparin (LMWH)		0/138 (0%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/83 (0%)
	Fondaparinux (FXaI)		0/84 (0%)
	Enoxaparin (LMWH)		0/83 (0%)
PE, Symptomatic			
Anderson 2013 23732713	Dalteparin (NA)	~100 days	3/398 (0.8%)
	Dalteparin then Aspirin (NA)		0/380 (0%)
Borgen 2012 22476844	Dalteparin (postop) (NA)	~8 days	1/40 (2.5%)
	Dalteparin (preop) (NA)		0/40 (0%)
Bramlage 2012 22713698	Certoparin 3000 IU (NA)	8-16 days	2/193 (1.0%)
	Certoparin 5000 IU (NA)		0/205 (0%)

Study	Arm	Timepoint	n/N (%)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (NA)	10 days	2/196 (1.0%)
	Enoxaparin (NA)		2/190 (1.1%)
	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	3 months	3/196 (1.5%)
	Enoxaparin (LMWH)		2/190 (1.1%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	0/120 (0%)
	Darexaban 5 mg (NA)		0/117 (0%)
	Enoxaparin 40 mg (LMWH)		0/127 (0%)
	Darexaban 120 mg (NA)		0/110 (0%)
	Darexaban 30 mg qD (NA)		0/114 (0%)
	Darexaban 10 mg (NA)		0/120 (0%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/72 (0%)
	Edoxaban 15 mg (NA)		0/78 (0%)
	Enoxaparin 20 mg BID (LMWH)		0/74 (0%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	0/163 (0%)
	Darexaban 15 mg BID (NA)		0/169 (0%)
	Darexaban 30 mg BID (FXaI)		1/174 (0.6%)
	Enoxaparin (LMWH)		0/103 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	0/255 (0%)
	Enoxaparin (LMWH)		0/248 (0%)
Kim 2016 26790579a	Placebo	2 days after treatment	1/185 (0.5)
	Rivaroxaban		1/184 (0.5)
	Enoxaparin		0/184 (0)
Kim 2016 26790579a	Placebo	4 weeks post-treatment	1/185 (0.5)
	Rivaroxaban		1/184 (0.5)
	Enoxaparin		0/184 (0)
Kim 2016 26790579b	Rivaroxaban	2 days after treatment days	1/166 (0.6)
	Enoxaparin		1/167 (0.6)

Study	Arm	Timepoint	n/N (%)
Kim 2016 26790579b	Rivaroxaban	4 weeks post-treatment	1/166 (0.6)
	Enoxaparin		1/167 (0.6)
Raskob 2010 20589317	Edoxaban 90 mg (NA)	7-10 days	0/151 (0%)
	Edoxaban 60 mg (NA)		1/158 (0.6%)
	Edoxaban 30 mg (FXaI)		0/151 (0%)
	Edoxaban 15 mg (NA)		0/170 (0%)
	Dalteparin 5000 IU (LMWH)		0/144 (0%)
Sakai 2016 26735531	Edoxaban	28 days	0/62 (0)
	Edoxaban + foot pump		0/58 (0)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	0/193 (0%)
	TB-402 25 mg (NA)		0/187 (0%)
	Rivaroxaban 10 mg (FXaI)		0/191 (0%)
PE, Total			
2014 NCT00246025	Dabigatran Etexilate 110 mg	2 weeks (treatment period)	0/133 (0)
	Dabigatran Etexilate 150 mg		0/126 (0)
	Dabigatran Etexilate 220 mg		0/129 (0)
Alfaro 1986 3535158	Aspirin 125 mg (Antiplatelet)	Post-operative days	0/30 (0%)
	Control (Placebo)		1/30 (3.3%)
	Aspirin 500 mg (NA)		0/30 (0%)
Andersen 1997 9690480	Dalteparin 35 days (NA)	35 days	0/20 (0%)
	Dalteparin 5-7 days (NA)		1/21 (4.8%)
Avikainen 1995 7645915	Heparin (UFH)	Post-operative days	1/84 (1.2%)
	Enoxaparin (LMWH)		0/83 (0%)
Barre 1987 2834500	Dalteparin (LMWH)	60 days	0/40 (0%)
	Heparin (UFH)		0/40 (0%)
Colwell 1994 8288662	Enoxaparin 40 mg (NA)	Post-operative days	0/203 (0%)
	Enoxaparin 30 mg (NA)		0/195 (0%)
	Heparin (NA)		1/209 (0.5%)
	Enoxaparin 40 mg (LMWH)	42 days	0/203 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin 30 mg (NA)		0/195 (0%)
	Heparin (UFH)		4/209 (1.9%)
Colwell 1999 10428124	Warfarin (VKA)	90 days	12/1495 (0.8%)
	Enoxaparin (LMWH)		15/1516 (1.0%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	1/211 (0.5%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/224 (0%)
Dahl 1997 9031444	Dalteparin 35 days (NA)	7-35 days	4/111 (3.6%)
	Dalteparin 7 days (NA)		7/106 (6.6%)
Edwards 2008 18534421 THA	Enoxaparin + IPC (LMWH_Mechanical)	90 days	0/65 (0%)
	Enoxaparin (LMWH)		0/59 (0%)
Eriksson 1991 2013587	Dalteparin (LMWH)	Post-operative days	8/65 (12%)
	Heparin (UFH)		19/62 (31%)
Eriksson 1996 8596376	Desirudin (DTI)	post-operative days	1/202 (0.5%)
	Heparin (UFH)		0/229 (0%)
Eriksson 1997A 9070519	Desirudin (DTI)	42 days	0/180 (0%)
	Heparin (UFH)		4/180 (2.2%)
Eriksson 1997B 9358126	Desirudin (NA)	Post-operative days	2/802 (0.2%)
	Enoxaparin (NA)		2/785 (0.3%)
	Desirudin (DTI)	42 days	3/802 (0.4%)
	Enoxaparin (LMWH)		7/785 (0.9%)
Eriksson 2007B 17869635	Dabigatran 150mg (NA)	Post-operative days	1/1156 (0.1%)
	Dabigatran 220mg (DTI)		5/1137 (0.4%)
	Enoxaparin (LMWH)		3/1142 (0.3%)
Fuji 2008 18843459 THA	Placebo (Placebo)	post-operative years	0/86 (0%)
	Enoxaparin 40 mg (LMWH)		1/80 (1.3%)
	Enoxaparin 20 mg (NA)		0/90 (0%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	90 days	1/398 (0.3%)
	Warfarin (VKA)		0/397 (0%)
Hull 2000 10904464	Warfarin (VKA)	post-operative days	0/489 (0%)

Study	Arm	Timepoint	n/N (%)
	Dalteparin preoperative (NA)		0/496 (0%)
	Dalteparin postoperative (LMWH)		0/487 (0%)
Lassen 1991 1848385	Placebo (Placebo)	Post-operative days	1/97 (1.0%)
	Tinzaparin (LMWH)		1/93 (1.1%)
Lassen 2002 12049858	Fondaparinux (FXaI)	49 days	2/1129 (0.2%)
	Enoxaparin (LMWH)		2/1123 (0.2%)
Lassen 2010A 21175312	Apixaban (NA)	~34 (on treatment) days	3/2708 (0.1%)
	Enoxaparin (NA)		5/2699 (0.2%)
	Apixaban (FXaI)	~94 (post-treatment) days	3/2708 (0.1%)
	Enoxaparin (LMWH)		9/2699 (0.3%)
Levine 1991 1848054	Heparin (UFH)	Post-operative days	2/332 (0.6%)
	Enoxaparin (LMWH)		0/333 (0%)
Lieberman 1994 8126039	Aspirin (Antiplatelet)	90 days	1/118 (0.8%)
	Aspirin+IPC (Antiplatelet_Mechanical)		1/113 (0.9%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	2/131 (1.5%)
	Enoxaparin 30 days (NA)		0/131 (0%)
Paiement 1987 3572408	IPC (Mechanical)	Post-operative days	0/66 (0%)
	Warfarin (VKA)		0/72 (0%)
Planes 1988 2853459	Heparin (UFH)	Post-operative days	1/108 (0.9%)
	Enoxaparin (LMWH)		0/120 (0%)
Planes 1997 9048403	Enoxaparin 21 days post-discharge (NA)	35 days	0/85 (0%)
	Enoxaparin to discharge (NA)		0/88 (0%)
Planès 1999 10348714	Tinzaparin (NA)	Post-operative days	1/251 (0.4%)
	Enoxaparin (NA)		2/248 (0.8%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	28 days	0/184 (0%)
	Warfarin until hospital discharge (NA)		1/176 (0.6%)
Ryan 2002 12429761	IPC (Venaflow) (NA)	post-operative days	0/50 (0%)
	GCS (T.E.D.) (NA)		0/50 (0%)
Sakai 2016 26735531	Edoxaban	28 days	0/62 (0)

Study	Arm	Timepoint	n/N (%)
	Edoxaban + foot pump		0/58 (0)
Samama 1997 9215015	Placebo (Placebo)	10 +/- 2 days	0/84 (0%)
	Enoxaparin (LMWH)		0/85 (0%)
Schwartsmann 1996 Embase 1996366023	Heparin (UFH)	Post-operative days	0/47 (0%)
	Enoxaparin (LMWH)		0/52 (0%)
Senaran 2006 16333632	Heparin (UFH)	42 days	0/50 (0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 1986 3531851	Placebo (Placebo)	Post-operative days	1/50 (2.0%)
	Enoxaparin (LMWH)		0/50 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	49 days	12/1126 (1.1%)
	Enoxaparin (LMWH)		4/1128 (0.4%)
Warwick 1995 7559695	Control (Placebo)	Post-operative days	2/78 (2.6%)
	Enoxaparin (LMWH)		1/78 (1.3%)
Warwick 1998 9730125	VFP (AV Impulse system) (Mechanical)	post-operative days	1/136 (0.7%)
	Enoxaparin (LMWH)		0/138 (0%)
Welin-Berger 1982 6184938	Heparin (UFH)	Post-operative days	0/20 (0%)
	Control (Placebo)		1/20 (5.0%)
Woolson 1991 2013589	IPC+ Aspirin (Antiplatelet_Mechanical)	Post-operative days	1/70 (1.4%)
	IPC (Mechanical)		0/73 (0%)
	IPC+ wafarin (VKA_Mechanical)		0/69 (0%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/83 (0%)
	Fondaparinux (FXaI)		0/84 (0%)
	Enoxaparin (LMWH)		0/83 (0%)
Return to OR, bleeding or infection (combined)			
Andersen 1997 9690480	Dalteparin 35 days (NA)	35 days	0/20 (0%)
	Dalteparin 5-7 days (NA)		2/21 (10%)
VTE, Symptomatic			
Anderson 2013 23732713	Dalteparin (NA)	~100 days	6/398 (1.5%)

Study	Arm	Timepoint	n/N (%)
	Dalteparin then Aspirin (NA)		1/380 (0.3%)
Colwell 1999 10428124	Warfarin (VKA)	90 days	56/1495 (3.7%)
	Enoxaparin (LMWH)		55/1516 (3.6%)
Comp 2001 11263636 THR	Enoxaparin 7-10 days (NA)	30 days	49/211 (23%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		18/224 (8.0%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	1/120 (0.8%)
	Darexaban 5 mg (NA)		1/117 (0.9%)
	Enoxaparin 40 mg (LMWH)		0/127 (0%)
	Darexaban 120 mg (NA)		1/110 (0.9%)
	Darexaban 30 mg qD (NA)		0/114 (0%)
	Darexaban 10 mg (NA)		1/120 (0.8%)
Eriksson 2011 21225098	Dabigatran 220 mg (NA)	28-35 (during treatment period) days	1/1001 (0.1%)
	Enoxaparin (NA)		6/992 (0.6%)
	Dabigatran 220 mg (DTI)	3 (treatment + follow-up) months	3/1001 (0.3%)
	Enoxaparin (LMWH)		8/992 (0.8%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	0/72 (0%)
	Edoxaban 15 mg (NA)		0/78 (0%)
	Enoxaparin 20 mg BID (LMWH)		0/74 (0%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	0/255 (0%)
	Enoxaparin (LMWH)		0/248 (0%)
Hull 1993 8413432 THA	Tinzaparin (LMWH)	90 days	6/398 (1.5%)
	Warfarin (VKA)		2/397 (0.5%)
Lassen 2002 12049858	Fondaparinux (FXaI)	49 days	12/1129 (1.1%)
	Enoxaparin (LMWH)		9/1123 (0.8%)
Nilsson 1997 9048404	Enoxaparin 9 days (NA)	30 days	10/131 (7.6%)
	Enoxaparin 30 days (NA)		2/131 (1.5%)
Prandoni 2002 12230419	Warfarin 28 days (NA)	90 days	3/184 (1.6%)
	Warfarin until hospital discharge (NA)		9/176 (5.1%)

Study	Arm	Timepoint	n/N (%)
Sakai 2016 26735531	Edoxaban	28 days	1/62 (1.6)
	Edoxaban + foot pump		3/58 (5.2)
Senaran 2006 16333632	Heparin (UFH)	42 days	2/50 (4.0%)
	Enoxaparin (LMWH)		2/50 (4.0%)
	Heparin (NA)	post-operative until discharge days	2/50 (4.0%)
	Enoxaparin (NA)		0/50 (0%)
Turpie 2002 12049860	Fondaparinux (FXaI)	49 days	29/1126 (2.6%)
	Enoxaparin (LMWH)		13/1128 (1.2%)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	0/193 (0%)
	TB-402 25 mg (NA)		0/187 (0%)
	Rivaroxaban 10 mg (FXaI)		0/191 (0%)
Yokote 2011 21282767	Placebo (Placebo)	11 days	0/83 (0%)
	Fondaparinux (FXaI)		1/84 (1.2%)
	Enoxaparin (LMWH)		0/83 (0%)
VTE, Total			
2013 NCT00595426	Wafarin	14 days (treatment duration)	24/133 (18)
	Darexaban 60 mg QD		12/137 (8.8)
	Darexaban 30 mg BID		21/137 (15.3)
	Darexaban 60 mg BID		9/138 (6.5)
	Darexaban 120 mg QD		9/141 (6.4)
Colwell 2010 20194309	Continuous Enhanced Circulation Therapy + Synchronized Flow Technology (Mechanical)	3 months	10/196 (5.1%)
	Enoxaparin (LMWH)		10/190 (5.3%)
Eriksson 2010 20088935	Darexaban 60 mg qD (FXaI)	9 days	16/120 (13%)
	Darexaban 5 mg (NA)		32/117 (27%)
	Enoxaparin 40 mg (LMWH)		24/127 (19%)
	Darexaban 120 mg (NA)		15/110 (14%)
	Darexaban 30 mg qD (NA)		22/114 (19%)
	Darexaban 10 mg (NA)		38/120 (32%)

Study	Arm	Timepoint	n/N (%)
Eriksson 2014 24136153	Enoxaparin 40 mg qD (LMWH)	12 days	48/314 (15%)
	Darexaban 30 mg qD (NA)		39/293 (13%)
	Darexaban 60 mg qD (FXaI)		36/274 (13%)
	Darexaban 30 mg BID (NA)		33/296 (11%)
	Darexaban 15 mg BID (NA)		42/269 (16%)
Fuji 2014A 25047458	Edoxaban 30 mg (FXaI)	11-14 days	2/72 (2.8%)
	Edoxaban 15 mg (NA)		3/78 (3.8%)
	Enoxaparin 20 mg BID (LMWH)		3/74 (4.1%)
Fuji 2014D 22952213 THA	Placebo (Placebo)	10-14 (during treatment period) days	22/129 (17%)
	Darexaban 15 mg BID (NA)		4/136 (2.9%)
	Darexaban 30 mg BID (FXaI)		7/134 (5.2%)
	Enoxaparin (LMWH)		2/82 (2.4%)
Fuji 2015 26269694	Edoxaban (FXaI)	11-14 days	6/255 (2.4%)
	Enoxaparin (LMWH)		17/248 (6.9%)
Lassen 2010A 21175312	Apixaban (FXaI)	~34 (on treatment) days	10/2199 (0.5%)
	Enoxaparin (LMWH)		25/2195 (1.1%)
Raskob 2010 20589317	Edoxaban 90 mg (NA)	7-10 days	16/151 (11%)
	Edoxaban 60 mg (NA)		24/158 (15%)
	Edoxaban 30 mg (FXaI)		32/151 (21%)
	Edoxaban 15 mg (NA)		48/170 (28%)
	Dalteparin 5000 IU (LMWH)		63/144 (44%)
Sakai 2016 26735531	Edoxaban	28 days	11/62 (17.7)
	Edoxaban + foot pump		18/58 (31)
Verhamme 2013 23615791	TB-402 50 mg (FViiiI)	35 days	10/193 (5.2%)
	TB-402 25 mg (NA)		10/187 (5.3%)
	Rivaroxaban 10 mg (FXaI)		9/191 (4.7%)

Table F2. RCT total knee replacement

Study	Arm	Timepoint	n/N (%)
Adherent/Compliant			
Choi 2015 24408881	Pneumatic compression with adjusted cycling rate (NA)	16.4 (full hospitalization) days	27/27 (100%)
	Pneumatic compression with fixed cycling rate (NA)		27/27 (100%)
Bleeding, Fatal			
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	0/517 (0%)
	Enoxaparin (LMWH)		0/517 (0%)
Cho 2013 23381297	Placebo (Placebo)	90 days	0/74 (0%)
	Fondaparinux (FXaI)		0/74 (0%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	0/221 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/217 (0%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/76 (0%)
	Enoxaparin (LMWH)		0/77 (0%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	90 days	0/703 (0%)
	Enoxaparin (LMWH)		0/694 (0%)
	Dabigatran 220 mg (DTI)		0/679 (0%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	1/176 (0.6%)
	Enoxaparin (LMWH)		0/173 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		0/124 (0%)
	Dabigatran 220 mg (DTI)		0/129 (0%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	0/871 (0%)
	Enoxaparin (LMWH)		0/868 (0%)
	Dabigatran 220 mg (DTI)		0/857 (0%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	Post-operative days	0/317 (0%)
	Warfarin (VKA)		0/324 (0%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	0/206 (0%)
	IPC (Kendal) (NA)		0/217 (0%)

Study	Arm	Timepoint	n/N (%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days days	0/573 (0%)
	Enoxaparin (NA)		0/568 (0%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	0/334 (0%)
	Enoxaparin (LMWH)		0/336 (0%)
McKenna 1980 6989432	Placebo (Placebo)	Post-operative days	0/12 (0%)
	Aspirin (Antiplatelet)		0/9 (0%)
Warwick 2002 12002490	VFP (AV Impulse system) (Mechanical)	post-operative days	0/117 (0%)
	Enoxaparin (LMWH)		0/112 (0%)
Bleeding, Leading to reoperation			
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	2/517 (0.4%)
	Enoxaparin (LMWH)		1/517 (0.2%)
Cho 2013 23381297	Placebo (Placebo)	90 days	0/74 (0%)
	Fondaparinux (FXaI)		0/74 (0%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	90 days	1/703 (0.1%)
	Enoxaparin (LMWH)		1/694 (0.1%)
	Dabigatran 220 mg (DTI)		3/679 (0.4%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	0/176 (0%)
	Enoxaparin (LMWH)		0/173 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		0/124 (0%)
	Dabigatran 220 mg (DTI)		1/129 (0.8%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	0/871 (0%)
	Enoxaparin (NA)		1/868 (0.1%)
	Dabigatran 220 mg (NA)		0/857 (0%)
Bleeding, Major			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	3/422 (0.7%)
	Anticoagulation (mixed) 10+-2 days (NA)		2/420 (0.5%)
	Anticoagulation (mixed) 35+-5 days (NA)	3 months	3/422 (0.7%)

Study	Arm	Timepoint	n/N (%)
	Anticoagulation (mixed) 10+-2 days (NA)		3/420 (0.7%)
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	11/517 (2.1%)
	Enoxaparin (LMWH)		1/517 (0.2%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~3 months	1/77 (1.3%)
	Enoxaparin (LMWH)		0/72 (0%)
	FXI-ASO 200 (FXiI)		0/144 (0%)
Cho 2013 23381297	Placebo (Placebo)	90 days	0/74 (0%)
	Fondaparinux (FXaI)		0/74 (0%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	1/202 (0.5%)
	Enoxaparin 30 mg BID (LMWH)		3/397 (0.8%)
	Eribaxaban 2.5 mg (NA)		1/200 (0.5%)
	Eribaxaban 10 mg (NA)		1/65 (1.5%)
	Eribaxaban 0.1 mg (NA)		0/61 (0%)
	Eribaxaban 4 mg (NA)		0/140 (0%)
	Eribaxaban 0.5 mg (NA)		2/183 (1.1%)
	Eribaxaban 0.3 mg (NA)		0/141 (0%)
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	3/225 (1.3%)
	Enoxaparin (LMWH)		3/228 (1.3%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	1/221 (0.5%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/217 (0%)
Eriksson 2005 15634273 TKA	Dabigatran 150 mg (DTI)	post-operative years	6/124 (4.8%)
	Dabigatran 300 mg (NA)		6/127 (4.7%)
	Enoxaprin (LMWH)		2/122 (1.6%)
	Dabigatran 50 mg (NA)		1/124 (0.8%)
	Dabigatran 225 mg (NA)		3/123 (2.4%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	90 days	9/703 (1.3%)
	Enoxaparin (LMWH)		9/694 (1.3%)
	Dabigatran 220 mg (DTI)		10/679 (1.5%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	4/176 (2.3%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		9/173 (5.2%)
Fuji 2008 18843459 TKA	Placebo (Placebo)	post-operative years	4/89 (4.5%)
	Enoxaparin 40 mg (LMWH)		1/91 (1.1%)
	Enoxaparin 20 mg (NA)		3/95 (3.2%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		1/124 (0.8%)
	Dabigatran 220 mg (DTI)		3/129 (2.3%)
Fuji 2010B 20723033	Placebo (Placebo)	11-14 days	0/102 (0%)
	Edoxaban 60 mg (NA)		1/106 (0.9%)
	Edoxaban 30 mg (FXaI)		0/103 (0%)
	Edoxaban 15 mg (NA)		0/106 (0%)
	Edoxaban 5 mg (NA)		0/103 (0%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	4/354 (1.1%)
	Enoxaparin (LMWH)		1/349 (0.3%)
Fuji 2014D 22952213 TKA	Placebo (NA)	10-14 (during treatment period) days	0/96 (0%)
	Darexaban 15 mg BID (NA)		0/92 (0%)
	Darexaban 30 mg BID (NA)		1/88 (1.1%)
	Enoxaparin (NA)		0/90 (0%)
	Placebo (Placebo)	3-5 weeks after the last dose (till study ended) weeks	0/96 (0%)
	Darexaban 15 mg BID (NA)		0/92 (0%)
	Darexaban 30 mg BID (FXaI)		1/88 (1.1%)
	Enoxaparin (LMWH)		0/90 (0%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post study period to 90 days	2/871 (0.2%)
	Enoxaparin (NA)		0/868 (0%)
	Dabigatran 220 mg (NA)		1/857 (0.1%)
	Dabigatran 150 mg (NA)	post-operative (in study period) days	5/871 (0.6%)
	Enoxaparin (LMWH)		12/868 (1.4%)
	Dabigatran 220 mg (DTI)		5/857 (0.6%)

Study	Arm	Timepoint	n/N (%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	Post-operative days	9/317 (2.8%)
	Warfarin (VKA)		3/324 (0.9%)
Iliopoulos 2011 Abstract P104	Dabigatran 110 mg (DTI)	5 days	0/40 (0%)
	Tinzaparin (NA)		0/40 (0%)
	Fondaparinux (FXaI)		0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
Lassen 2007 17868430	Warfarin (VKA)	Post-operative years	0/151 (0%)
	Enoxaparin (LMWH)		0/149 (0%)
Lassen 2010B 20206776	Apixaban (FXaI)	NR	9/1501 (0.6%)
	Enoxaparin (LMWH)		14/1508 (0.9%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days days	3/573 (0.5%)
	Enoxaparin (NA)		4/568 (0.7%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	6/334 (1.8%)
	Enoxaparin (LMWH)		7/336 (2.1%)
Mirdamadi 2014 25815018	Dabigatran 225 mg (DTI)	15 days	3/45 (6.7%)
	Enoxaparin (LMWH)		2/45 (4.4%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	90 days	0/75 (0%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		1/74 (1.4%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		4/87 (4.6%)
	Enoxaparin (NA)		0/79 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	0/162 (0%)
	TAK-442 40 BID (FXaI)		2/162 (1.2%)
	TAK-442 80 BID (NA)		0/161 (0%)
	TAK-442 10 (NA)		0/104 (0%)
	TAK-442 20 (NA)		1/128 (0.8%)
	TAK-442 80 qD (NA)		1/160 (0.6%)
	Enoxaparin (LMWH)		3/161 (1.9%)
Westrich 1996 8666599	Aspirin (NA)	Post-operative days	0/61 (0%)

Study	Arm	Timepoint	n/N (%)
	Aspirin+ VFP (NA)		0/61 (0%)
Bleeding, Surgical site/joint			
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	5/225 (2.2%)
	Enoxaparin (LMWH)		9/228 (3.9%)
Fitzgerald 2001 11407799	Warfarin (VKA)	Post-operative days	6/176 (3.4%)
	Enoxaparin (LMWH)		12/173 (6.9%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	6/354 (1.7%)
	Enoxaparin (LMWH)		2/349 (0.6%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	3/871 (0.3%)
	Enoxaparin (LMWH)		11/868 (1.3%)
	Dabigatran 220 mg (DTI)		2/857 (0.2%)
Lassen 2010B 20206776	Apixaban (FXaI)	nd days	8/1501 (0.5%)
	Enoxaparin (LMWH)		11/1508 (0.7%)
DVT, Proximal			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	4/422 (0.9%)
	Anticoagulation (mixed) 10+-2 days (NA)		6/420 (1.4%)
	Anticoagulation (mixed) 35+-5 days (NA)	3 months	4/422 (0.9%)
	Anticoagulation (mixed) 10+-2 days (NA)		6/420 (1.4%)
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	9/368 (2.4%)
	Enoxaparin (LMWH)		20/372 (5.4%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	1/71 (1.4%)
	Enoxaparin (LMWH)		5/71 (7.0%)
	FXI-ASO 200 (FXiI)		7/139 (5.0%)
Chin 2009 19398783	Control (Placebo)	Post-operative days	3/110 (2.7%)
	Enoxaparin (LMWH)		1/110 (0.9%)
Cho 2013 23381297	Placebo (NA)	7 days	4/74 (5.4%)
	Fondaparinux (NA)		1/74 (1.4%)
	Placebo (Placebo)	90 days	4/74 (5.4%)
	Fondaparinux (FXaI)		1/74 (1.4%)

Study	Arm	Timepoint	n/N (%)
Choi 2015 24408881	Pneumatic compression with adjusted cycling rate (NA)	5 days	1/27 (3.7%)
	Pneumatic compression with fixed cycling rate (NA)		1/27 (3.7%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	4/120 (3.3%)
	Enoxaparin 30 mg BID (LMWH)		4/188 (2.1%)
	Eribaxaban 2.5 mg (NA)		2/112 (1.8%)
	Eribaxaban 10 mg (NA)		1/27 (3.7%)
	Eribaxaban 0.1 mg (NA)		2/35 (5.7%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		4/104 (3.8%)
	Eribaxaban 0.3 mg (NA)		3/89 (3.4%)
	Eribaxaban 1 mg (FXaI)	~40 days	4/120 (3.3%)
	Enoxaparin 30 mg BID (LMWH)		5/188 (2.7%)
	Eribaxaban 2.5 mg (NA)		2/112 (1.8%)
	Eribaxaban 10 mg (NA)		1/27 (3.7%)
	Eribaxaban 0.1 mg (NA)		2/35 (5.7%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		4/104 (3.8%)
	Eribaxaban 0.3 mg (NA)		3/89 (3.4%)
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	22/225 (10%)
	Enoxaparin (LMWH)		5/228 (2.2%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	17/221 (7.7%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		9/217 (4.1%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/76 (0%)
	Enoxaparin (LMWH)		0/77 (0%)
Eriksson 2005 15634273 TKA	Dabigatran 150 mg (DTI)	post-operative years	1/81 (1.2%)
	Dabigatran 300 mg (NA)		3/92 (3.3%)
	Enoxaprin (LMWH)		6/92 (6.5%)
	Dabigatran 50 mg (NA)		3/94 (3.2%)

Study	Arm	Timepoint	n/N (%)
	Dabigatran 225 mg (NA)		1/93 (1.1%)
Faunø 1994 7989386	Heparin (UFH)	Post-operative days	5/93 (5.4%)
	Enoxaparin (LMWH)		3/92 (3.3%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	20/176 (11%)
	Enoxaparin (LMWH)		3/173 (1.7%)
Fuji 2008 18843459 TKA	Placebo (Placebo)	post-operative years	6/79 (7.6%)
	Enoxaparin 40 mg (LMWH)		3/74 (4.1%)
	Enoxaparin 20 mg (NA)		0/84 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	2/113 (1.8%)
	Placebo (Placebo)		6/104 (5.8%)
	Dabigatran 220 mg (DTI)		0/102 (0%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	1/88 (1.1%)
	Edoxaban 30 mg (NA)		1/88 (1.1%)
	Edoxaban 15 mg (NA)		0/92 (0%)
	Edoxaban 5 mg (NA)		0/87 (0%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	0/299 (0%)
	Enoxaparin (LMWH)		1/295 (0.3%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	3/70 (4.3%)
	Darexaban 15 mg BID (NA)		5/83 (6.0%)
	Darexaban 30 mg BID (FXaI)		1/74 (1.4%)
	Enoxaparin (LMWH)		1/74 (1.4%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	20/649 (3.1%)
	Enoxaparin (LMWH)		10/643 (1.6%)
	Dabigatran 220 mg (DTI)		14/604 (2.3%)
Haas 1990 2404020	Aspirin (Antiplatelet)	Post-operative days	1/58 (1.7%)
	IPC (Mechanical)		2/61 (3.3%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	Post-operative days	20/258 (7.8%)
	Warfarin (VKA)		34/277 (12%)
Jiang 2014 24931228	Aspirin (NA)	5 days	1/60 (1.7%)

Study	Arm	Timepoint	n/N (%)
	LMWH then rivaroxaban (NA)		1/60 (1.7%)
Koo 2014 25436073	alternate sequential compression device (SCD Express) (NA)	4 days	0/13 (0%)
	simultaneous sequential compression device (DVT-3000) (NA)		0/11 (0%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	1/232 (0.4%)
	IPC (Kendal) (NA)		6/240 (2.5%)
Lassen 2007 17868430	Warfarin (VKA)	Post-operative years	2/109 (1.8%)
	Enoxaparin (LMWH)		1/109 (0.9%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	7-11 days	17/483 (3.5%)
	Enoxaparin (NA)		10/487 (2.1%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	22/334 (6.6%)
	Enoxaparin (LMWH)		24/336 (7.1%)
Lotke 1996 8595765 TKA	Aspirin (Antiplatelet)	Post-operative days days	13/114 (11%)
	Warfarin (VKA)		8/75 (11%)
McKenna 1980 6989432	Placebo (Placebo)	Post-operative days	5/12 (42%)
	Aspirin (Antiplatelet)		3/9 (33%)
Silbersack 2004 15330019 TKA	Enoxaparin + GCS (Comprinet Pro) (NA)	6th-12th post-operative days	1/35 (2.9%)
	Enoxaparin + IPC (Venaflow) (NA)		0/35 (0%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	1/72 (1.4%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		0/79 (0%)
	Enoxaparin (NA)		3/77 (3.9%)
	Enoxaparin then TB-402 0.3 mg/kg (NA)	90 days	1/72 (1.4%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		0/79 (0%)
	Enoxaparin (NA)		4/77 (5.2%)
Warwick 2002 12002490	VFP (AV Impulse system) (Mechanical)	post-operative days	4/99 (4.0%)
	Enoxaparin (LMWH)		0/89 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	4/115 (3.5%)

Study	Arm	Timepoint	n/N (%)
	TAK-442 40 BID (FXaI)		4/112 (3.6%)
	TAK-442 80 BID (NA)		1/119 (0.8%)
	TAK-442 10 (NA)		2/77 (2.6%)
	TAK-442 20 (NA)		4/86 (4.7%)
	TAK-442 80 qD (NA)		3/112 (2.7%)
	Enoxaparin (LMWH)		3/109 (2.8%)
Westrich 1996 8666599	Aspirin (Antiplatelet)	Post-operative days	5/39 (13%)
	Aspirin+ VFP (Antiplatelet_Mechanical)		0/41 (0%)
Wilson 1992 1732265	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative days	0/28 (0%)
	Control (Placebo)		6/32 (19%)
DVT, Symptomatic			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	2/422 (0.5%)
	Anticoagulation (mixed) 10+-2 days (NA)		7/420 (1.7%)
	Anticoagulation (mixed) 35+-5 days (NA)	3 months	2/422 (0.5%)
	Anticoagulation (mixed) 10+-2 days (NA)		7/420 (1.7%)
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	3/517 (0.6%)
	Enoxaparin (LMWH)		4/517 (0.8%)
Bonneux 2006 16387501	Fondaparinux (FXaI)	Post-operative days	2/55 (3.6%)
	Enoxaparin (LMWH)		1/54 (1.9%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	0/71 (0%)
	Enoxaparin (NA)		1/71 (1.4%)
	FXI-ASO 200 (NA)		2/139 (1.4%)
	FXI-ASO 300 (NA)	~3 months	0/71 (0%)
	Enoxaparin (LMWH)		1/71 (1.4%)
	FXI-ASO 200 (FXiI)		2/139 (1.4%)
Cho 2013 23381297	Placebo (NA)	7 days	0/74 (0%)
	Fondaparinux (NA)		0/74 (0%)
	Placebo (Placebo)	90 days	0/74 (0%)

Study	Arm	Timepoint	n/N (%)
	Fondaparinux (FXaI)		0/74 (0%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	0/120 (0%)
	Enoxaparin 30 mg BID (LMWH)		1/188 (0.5%)
	Eribaxaban 2.5 mg (NA)		0/112 (0%)
	Eribaxaban 10 mg (NA)		0/27 (0%)
	Eribaxaban 0.1 mg (NA)		0/35 (0%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		1/104 (1.0%)
	Eribaxaban 0.3 mg (NA)		0/89 (0%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	90 days	3/696 (0.4%)
	Enoxaparin (LMWH)		8/685 (1.2%)
	Dabigatran 220 mg (DTI)		1/675 (0.1%)
Faunø 1994 7989386	Heparin (UFH)	60 days	1/93 (1.1%)
	Enoxaparin (LMWH)		0/92 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	2/126 (1.6%)
	Placebo (Placebo)		2/124 (1.6%)
	Dabigatran 220 mg (DTI)		1/129 (0.8%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	0/88 (0%)
	Edoxaban 30 mg (NA)		0/88 (0%)
	Edoxaban 15 mg (NA)		0/92 (0%)
	Edoxaban 5 mg (NA)		1/88 (1.1%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	4/299 (1.3%)
	Enoxaparin (LMWH)		1/295 (0.3%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	0/96 (0%)
	Darexaban 15 mg BID (NA)		1/91 (1.1%)
	Darexaban 30 mg BID (FXaI)		0/88 (0%)
	Enoxaparin (LMWH)		1/90 (1.1%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	6/649 (0.9%)
	Enoxaparin (LMWH)		5/643 (0.8%)

Study	Arm	Timepoint	n/N (%)
	Dabigatran 220 mg (DTI)		7/604 (1.2%)
Jiang 2014 24931228	Aspirin (NA)	5 days	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
	Aspirin (NA)	6 weeks	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
Koo 2014 25436073	alternate sequential compression device (SCD Express) (NA)	4 days	0/13 (0%)
	simultaneous sequential compression device (DVT-3000) (NA)		0/11 (0%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	discharge-180 days	0/206 (0%)
	IPC (Kendal) (NA)		0/217 (0%)
Lassen 2007 17868430	Warfarin (VKA)	Post-operative years	1/109 (0.9%)
	Enoxaparin (LMWH)		1/109 (0.9%)
Lassen 2010B 20206776	Apixaban (NA)	10-14 (during intended treatment) days	3/1528 (0.2%)
	Enoxaparin (NA)		7/1529 (0.5%)
	Apixaban (FXaI)	30-60 after completion of treatment (during intended treatment and follow-up) days	5/1528 (0.3%)
	Enoxaparin (LMWH)		7/1529 (0.5%)
Mirdamadi 2014 25815018	Dabigatran 225 mg (DTI)	15 days	1/45 (2.2%)
	Enoxaparin (LMWH)		1/45 (2.2%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	0/72 (0%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		1/79 (1.3%)
	Enoxaparin (NA)		0/77 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	1/115 (0.9%)
	TAK-442 40 BID (FXaI)		4/112 (3.6%)
	TAK-442 80 BID (NA)		1/119 (0.8%)
	TAK-442 10 (NA)		1/77 (1.3%)
	TAK-442 20 (NA)		1/86 (1.2%)
	TAK-442 80 qD (NA)		1/112 (0.9%)
	Enoxaparin (LMWH)		2/109 (1.8%)

Study	Arm	Timepoint	n/N (%)
Windisch 2011 20652250	Enoxaparin + A-V Impulse (AVI) (LMWH_Mechanical)	8 days	0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
	Enoxaparin + A-V Impulse (AVI) (LMWH_Mechanical)	3 months	0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
Zou 2014 24695091	Aspirin (Antiplatelet)	4 weeks	2/110 (1.8%)
	Rivaroxaban (FXaI)		0/102 (0%)
	Enoxaparin (LMWH)		1/112 (0.9%)
DVT, Total			
Alkire 2010 20142693	Placebo (no device) (Placebo)	3 months	0/32 (0%)
	Continuous passive motion (Danniflex 480) (Mechanical)	3 months	0/32 (0%)
Bauer 2001 11794149	Fondaparinux (FXaI)	11 days	45/361 (12%)
	Enoxaparin (LMWH)	11 days	98/361 (27%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	3/71 (4.2%)
	Enoxaparin (LMWH)	~12 days	22/71 (31%)
	FXI-ASO 200 (FXiI)	~12 days	36/139 (26%)
Chin 2009 19398783	Control (Placebo)	Post-operative days	24/110 (22%)
	Enoxaparin (LMWH)	Post-operative days	6/110 (5.5%)
Cho 2013 23381297	Placebo (Placebo)	7 days	19/74 (26%)
	Fondaparinux (FXaI)	7 days	5/74 (6.8%)
	Placebo (NA)	90 days	19/74 (26%)
	Fondaparinux (NA)	90 days	5/74 (6.8%)
Choi 2015 24408881	Pneumatic compression with adjusted cycling rate (NA)	5 days	15/27 (56%)
	Pneumatic compression with fixed cycling rate (NA)	5 days	14/27 (52%)
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	77/225 (34%)
	Enoxaparin (LMWH)	Post-operative days	56/228 (25%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	46/221 (21%)
	Enoxaparin 7-10 days+ 3 weeks (NA)	30 days	38/217 (18%)

Study	Arm	Timepoint	n/N (%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	5/76 (6.6%)
	Enoxaparin (LMWH)		8/77 (10%)
Eriksson 2005 15634273 TKA	Dabigatran 150 mg (DTI)	post-operative years	21/81 (26%)
	Dabigatran 300 mg (NA)		22/92 (24%)
	Enoxaprin (LMWH)		41/92 (45%)
	Dabigatran 50 mg (NA)		37/94 (39%)
	Dabigatran 225 mg (NA)		22/93 (24%)
Faunø 1994 7989386	Heparin (UFH)	Post-operative days	25/93 (27%)
	Enoxaparin (LMWH)		21/92 (23%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	79/176 (45%)
	Enoxaparin (LMWH)		44/173 (25%)
Fuji 2008 18843459 TKA	Placebo (Placebo)	post-operative years	48/79 (61%)
	Enoxaparin 40 mg (LMWH)		25/74 (34%)
	Enoxaparin 20 mg (NA)		25/84 (30%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	34/104 (33%)
	Placebo (Placebo)		57/101 (56%)
	Dabigatran 220 mg (DTI)		23/96 (24%)
Fuji 2010B 20723033	Placebo (Placebo)	11-14 days	43/89 (48%)
	Edoxaban 60 mg (NA)		8/88 (9.1%)
	Edoxaban 30 mg (FXaI)		11/88 (13%)
	Edoxaban 15 mg (NA)		24/92 (26%)
	Edoxaban 5 mg (NA)		25/87 (29%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	22/299 (7.4%)
	Enoxaparin (LMWH)		41/295 (14%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	38/72 (53%)
	Darexaban 15 mg BID (NA)		22/81 (27%)
	Darexaban 30 mg BID (FXaI)		11/71 (15%)
	Enoxaparin (LMWH)		14/66 (21%)
Haas 1990 2404020	Aspirin (Antiplatelet)	Post-operative days	32/58 (55%)

Study	Arm	Timepoint	n/N (%)
	IPC (Mechanical)		20/61 (33%)
Hu 2015 No PMID	Rivaroxaban (FXaI)	2 weeks	1/45 (2.2%)
	Enoxaparin (LMWH)		4/45 (8.9%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	Post-operative days	116/258 (45%)
	Warfarin (VKA)		152/277 (55%)
Iliopoulos 2011 Abstract P104	Dabigatran 110 mg (DTI)	5 days	0/40 (0%)
	Tinzaparin (NA)		0/40 (0%)
	Fondaparinux (FXaI)		0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
Jiang 2014 24931228	Aspirin (NA)	5 days	10/60 (17%)
	LMWH then rivaroxaban (NA)		11/60 (18%)
Koo 2014 25436073	alternate sequential compression device (SCD Express) (NA)	4 days	1/13 (7.7%)
	simultaneous sequential compression device (DVT-3000) (NA)		4/11 (36%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	16/232 (6.9%)
	IPC (Kendal) (NA)		36/240 (15%)
Lassen 2010B 20206776	Apixaban (FXaI)	10-14 (during intended treatment) days	142/971 (15%)
	Enoxaparin (LMWH)		243/997 (24%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	7-11 days	105/428 (25%)
	Enoxaparin (NA)		120/427 (28%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	109/334 (33%)
	Enoxaparin (LMWH)		76/336 (23%)
Lotke 1996 8595765 TKA	Aspirin (Antiplatelet)	Post-operative days days	76/114 (67%)
	Warfarin (VKA)		52/75 (69%)
McKenna 1980 6989432	Placebo (Placebo)	Post-operative days	9/12 (75%)
	Aspirin (Antiplatelet)		7/9 (78%)
Rader 1998 9526211 TKA	Heparin+ Enoxaparin (NA)	post-operative days	6/60 (10%)
	Heparin+ Heparin (NA)		1/60 (1.7%)
Silbersack 2004 15330019 TKA	Enoxaparin + GCS (Comprinet Pro) (NA)	6th-12th post-operative days	14/35 (40%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin + IPC (Venaflow) (NA)		0/35 (0%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	12/72 (17%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		16/67 (24%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		19/79 (24%)
	Enoxaparin (NA)		30/77 (39%)
	Enoxaparin then TB-402 0.3 mg/kg (NA)	90 days	12/72 (17%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		16/67 (24%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		19/79 (24%)
	Enoxaparin (NA)		31/77 (40%)
Warwick 2002 12002490	VFP (AV Impulse system) (Mechanical)	post-operative days	57/99 (58%)
	Enoxaparin (LMWH)		48/89 (54%)
Westrich 1996 8666599	Aspirin (Antiplatelet)	Post-operative days	26/39 (67%)
	Aspirin+ VFP (Antiplatelet_Mechanical)		11/41 (27%)
Wilson 1992 1732265	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative days	14/28 (50%)
	Control (Placebo)		22/32 (69%)
Windisch 2011 20652250	Enoxaparin + A-V Impulse (AVI) (LMWH_Mechanical)	8 days	0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
Zou 2014 24695091	Aspirin (Antiplatelet)	4 weeks	18/110 (16%)
	Rivaroxaban (FXaI)		3/102 (2.9%)
	Enoxaparin (LMWH)		14/112 (13%)
Heparin-induced thrombocytopenia			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	0/422 (0%)
	Anticoagulation (mixed) 10+-2 days (NA)		0/420 (0%)
Infection, Leading to reoperation			
Fitzgerald 2001 11407799	Warfarin (NA)	post-operative days	0/176 (0%)
	Enoxaparin (NA)		0/173 (0%)
Major adverse event, other			
Büller 2015 25482425	FXI-ASO 300 (NA)	~3 months	1/77 (1.3%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		0/72 (0%)
	FXI-ASO 200 (FXIl)		3/144 (2.1%)
Cho 2013 23381297	Placebo (Placebo)	90 days	0/74 (0%)
	Fondaparinux (FXaI)		0/74 (0%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	0/202 (0%)
	Enoxaparin 30 mg BID (LMWH)		3/397 (0.8%)
	Eribaxaban 2.5 mg (NA)		0/200 (0%)
	Eribaxaban 10 mg (NA)		2/65 (3.1%)
	Eribaxaban 0.1 mg (NA)		0/61 (0%)
	Eribaxaban 4 mg (NA)		0/140 (0%)
	Eribaxaban 0.5 mg (NA)		2/183 (1.1%)
	Eribaxaban 0.3 mg (NA)		2/141 (1.4%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	10/354 (2.8%)
	Enoxaparin (LMWH)		11/349 (3.2%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	1/96 (1.0%)
	Darexaban 15 mg BID (NA)		1/92 (1.1%)
	Darexaban 30 mg BID (FXaI)		3/88 (3.4%)
	Enoxaparin (LMWH)		2/90 (2.2%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days days	13/573 (2.3%)
	Enoxaparin (NA)		17/568 (3.0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	12/162 (7.4%)
	TAK-442 40 BID (FXaI)		7/162 (4.3%)
	TAK-442 80 BID (NA)		14/161 (8.7%)
	TAK-442 10 (NA)		9/104 (8.7%)
	TAK-442 20 (NA)		12/128 (9.4%)
	TAK-442 80 qD (NA)		12/160 (7.5%)
	Enoxaparin (LMWH)		16/161 (10%)
Mortality, 30 day or in-hospital (AE)			

Study	Arm	Timepoint	n/N (%)
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	0/422 (0%)
	Anticoagulation (mixed) 10+-2 days (NA)		0/420 (0%)
Bauer 2001 11794149	Fondaparinux (FXaI)	49 days	2/517 (0.4%)
	Enoxaparin (LMWH)		3/517 (0.6%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	0/221 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/217 (0%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	post-operative days	0/76 (0%)
	Enoxaparin (LMWH)		0/77 (0%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	90 days	1/696 (0.1%)
	Enoxaparin (LMWH)		1/685 (0.1%)
	Dabigatran 220 mg (DTI)		1/675 (0.1%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	3/176 (1.7%)
	Enoxaparin (LMWH)		1/173 (0.6%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		0/124 (0%)
	Dabigatran 220 mg (DTI)		0/129 (0%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	0/96 (0%)
	Darexaban 15 mg BID (NA)		0/92 (0%)
	Darexaban 30 mg BID (FXaI)		0/88 (0%)
	Enoxaparin (LMWH)		0/90 (0%)
Ginsberg 2009 18534438	Dabigatran 150 mg (NA)	post-operative years	1/871 (0.1%)
	Enoxaparin (NA)		0/868 (0%)
	Dabigatran 220 mg (NA)		1/857 (0.1%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	0/206 (0%)
	IPC (Kendal) (NA)		1/217 (0.5%)
Lassen 2010B 20206776	Apixaban (FXaI)	10-14 (during intended treatment) days	2/1528 (0.1%)
	Enoxaparin (LMWH)		0/1529 (0%)
Lassen 2012 22429800 TKA	Semuloparin (NA)	7-11 days	0/573 (0%)
	Enoxaparin (NA)		0/568 (0%)

Study	Arm	Timepoint	n/N (%)
McKenna 1980 6989432	Placebo (Placebo)	Post-operative days	0/12 (0%)
	Aspirin (Antiplatelet)		0/9 (0%)
Warwick 2002 12002490	VFP (AV Impulse system) (Mechanical)	post-operative days	3/117 (2.6%)
	Enoxaparin (LMWH)		1/112 (0.9%)
PE, Fatal			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	0/422 (0%)
	Anticoagulation (mixed) 10+-2 days (NA)		0/420 (0%)
	Anticoagulation (mixed) 35+-5 days (NA)	3 months	0/422 (0%)
	Anticoagulation (mixed) 10+-2 days (NA)		0/420 (0%)
Bauer 2001 11794149	Fondaparinux (FXaI)	49 days	1/517 (0.2%)
	Enoxaparin (LMWH)		1/517 (0.2%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	0/71 (0%)
	Enoxaparin (LMWH)		0/71 (0%)
	FXI-ASO 200 (FXiI)		0/139 (0%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	0/120 (0%)
	Enoxaparin 30 mg BID (LMWH)		0/188 (0%)
	Eribaxaban 2.5 mg (NA)		0/112 (0%)
	Eribaxaban 10 mg (NA)		0/27 (0%)
	Eribaxaban 0.1 mg (NA)		0/35 (0%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		0/104 (0%)
	Eribaxaban 0.3 mg (NA)		0/89 (0%)
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	1/225 (0.4%)
	Enoxaparin (LMWH)		0/228 (0%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	0/221 (0%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/217 (0%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	90 days	0/76 (0%)
	Enoxaparin (LMWH)		0/77 (0%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	Post-operative days	0/696 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		1/685 (0.1%)
	Dabigatran 220 mg (DTI)		0/675 (0%)
Faunø 1994 7989386	Heparin (UFH)	Post-operative days	0/93 (0%)
	Enoxaparin (LMWH)		0/92 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		0/124 (0%)
	Dabigatran 220 mg (DTI)		0/129 (0%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	0/88 (0%)
	Edoxaban 30 mg (NA)		0/88 (0%)
	Edoxaban 15 mg (NA)		0/92 (0%)
	Edoxaban 5 mg (NA)		0/88 (0%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	0/299 (0%)
	Enoxaparin (LMWH)		0/295 (0%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	90 days	0/317 (0%)
	Warfarin (VKA)		0/324 (0%)
Jiang 2014 24931228	Aspirin (NA)	5 days	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
	Aspirin (NA)	6 weeks	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	0/206 (0%)
	IPC (Kendal) (NA)		0/217 (0%)
Lassen 2007 17868430	Warfarin (VKA)	Post-operative years	0/109 (0%)
	Enoxaparin (LMWH)		0/109 (0%)
Lassen 2010B 20206776	Apixaban (NA)	10-14 (during intended treatment) days	1/1528 (0.1%)
	Enoxaparin (NA)		0/1529 (0%)
Lassen 2010B 20206776	Apixaban (FXaI)	30-60 after completion of treatment (during intended treatment and follow-up) years	2/1528 (0.1%)
	Enoxaparin (LMWH)		0/1529 (0%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	0/334 (0%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		0/336 (0%)
Mirdamadi 2014 25815018	Dabigatran 225 mg (DTI)	15 days	0/45 (0%)
	Enoxaparin (LMWH)		0/45 (0%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	0/72 (0%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		0/79 (0%)
	Enoxaparin (NA)		0/77 (0%)
Warwick 2002 12002490	VFP (AV Impulse system) (Mechanical)	post-operative days	2/117 (1.7%)
	Enoxaparin (LMWH)		0/112 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	0/115 (0%)
	TAK-442 40 BID (FXaI)		0/112 (0%)
	TAK-442 80 BID (NA)		0/119 (0%)
	TAK-442 10 (NA)		0/77 (0%)
	TAK-442 20 (NA)		0/86 (0%)
	TAK-442 80 qD (NA)		0/112 (0%)
	Enoxaparin (LMWH)		0/109 (0%)
Wilson 1992 1732265	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative days	0/28 (0%)
	Control (Placebo)		0/32 (0%)
PE, Symptomatic			
Barrellier 2010 20797774	Anticoagulation (mixed) 35+-5 days (NA)	~35 days	1/422 (0.2%)
	Anticoagulation (mixed) 10+-2 days (NA)		2/420 (0.5%)
	Anticoagulation (mixed) 35+-5 days (NA)	3 months	1/422 (0.2%)
	Anticoagulation (mixed) 10+-2 days (NA)		2/420 (0.5%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	0/71 (0%)
	Enoxaparin (NA)		0/71 (0%)
	FXI-ASO 200 (NA)		0/139 (0%)
	FXI-ASO 300 (NA)	~3 months	0/71 (0%)
	Enoxaparin (LMWH)		0/71 (0%)

Study	Arm	Timepoint	n/N (%)
	FXI-ASO 200 (FXiI)		0/139 (0%)
Cho 2013 23381297	Placebo (NA)	7 days	0/74 (0%)
	Fondaparinux (NA)		0/74 (0%)
Cho 2013 23381297	Placebo (Placebo)	90 days	0/74 (0%)
	Fondaparinux (FXaI)		0/74 (0%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	0/88 (0%)
	Edoxaban 30 mg (NA)		0/88 (0%)
	Edoxaban 15 mg (NA)		0/92 (0%)
	Edoxaban 5 mg (NA)		0/88 (0%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	0/299 (0%)
Fuji 2014C 25294589	Enoxaparin (LMWH)		0/295 (0%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	0/96 (0%)
	Darexaban 15 mg BID (NA)		0/92 (0%)
	Darexaban 30 mg BID (FXaI)		0/88 (0%)
	Enoxaparin (LMWH)		1/90 (1.1%)
Jiang 2014 24931228	Aspirin (NA)	5 days	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
	Aspirin (NA)	6 weeks	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
Mirdamadi 2014 25815018	Dabigatran 225 mg (DTI)	15 days	0/45 (0%)
	Enoxaparin (LMWH)		0/45 (0%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	0/72 (0%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		0/79 (0%)
	Enoxaparin (NA)		0/77 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	0/115 (0%)
	TAK-442 40 BID (FXaI)	10 days	1/112 (0.9%)
	TAK-442 80 BID (NA)		2/119 (1.7%)
	TAK-442 10 (NA)		1/77 (1.3%)

Study	Arm	Timepoint	n/N (%)
	TAK-442 20 (NA)		1/86 (1.2%)
	TAK-442 80 qD (NA)		0/112 (0%)
	Enoxaparin (LMWH)		2/109 (1.8%)
Windisch 2011 20652250	Enoxaparin + A-V Impulse (AVI) (LMWH_Mechanical)	8 days	0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
PE, Total			
Bauer 2001 11794149	Fondaparinux (FXaI)	49 days	3/517 (0.6%)
	Enoxaparin (LMWH)		5/517 (1.0%)
	Fondaparinux (NA)	11 days	1/517 (0.2%)
	Enoxaparin (NA)		4/517 (0.8%)
Chin 2009 19398783	Control (Placebo)	Post-operative days	1/110 (0.9%)
	Enoxaparin (LMWH)		0/110 (0%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	1/120 (0.8%)
	Enoxaparin 30 mg BID (LMWH)		3/188 (1.6%)
	Eribaxaban 2.5 mg (NA)		1/112 (0.9%)
	Eribaxaban 10 mg (NA)		0/27 (0%)
	Eribaxaban 0.1 mg (NA)		0/35 (0%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		0/104 (0%)
	Eribaxaban 0.3 mg (NA)		0/89 (0%)
	Eribaxaban 1 mg (FXaI)	~40 days	1/120 (0.8%)
	Enoxaparin 30 mg BID (LMWH)		4/188 (2.1%)
	Eribaxaban 2.5 mg (NA)		1/112 (0.9%)
	Eribaxaban 10 mg (NA)		0/27 (0%)
	Eribaxaban 0.1 mg (NA)		0/35 (0%)
	Eribaxaban 4 mg (NA)		0/74 (0%)
	Eribaxaban 0.5 mg (NA)		0/104 (0%)
	Eribaxaban 0.3 mg (NA)		0/89 (0%)

Study	Arm	Timepoint	n/N (%)
Colwell 1995 7497668	Heparin (UFH)	Post-operative days	2/225 (0.9%)
	Enoxaparin (LMWH)		0/228 (0%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	2/221 (0.9%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		0/217 (0%)
Edwards 2008 18534421 TKA	Enoxaparin + IPC (LMWH_Mechanical)	90 days	1/76 (1.3%)
	Enoxaparin (LMWH)		1/77 (1.3%)
Eriksson 2007A 17764540	Dabigatran 150 mg (NA)	Post-operative days	1/696 (0.1%)
	Enoxaparin (LMWH)		1/685 (0.1%)
	Dabigatran 220 mg (DTI)		0/675 (0%)
Faunø 1994 7989386	Heparin (UFH)	Post-operative days	0/93 (0%)
	Enoxaparin (LMWH)		0/92 (0%)
Fitzgerald 2001 11407799	Warfarin (VKA)	post-operative days	1/176 (0.6%)
	Enoxaparin (LMWH)		0/173 (0%)
Fuji 2008 18843459 TKA	Placebo (Placebo)	post-operative years	1/79 (1.3%)
	Enoxaparin 40 mg (LMWH)		1/74 (1.4%)
	Enoxaparin 20 mg (NA)		0/84 (0%)
Fuji 2010A 19854610	Dabigatran 150 mg (NA)	post-operative days	0/126 (0%)
	Placebo (Placebo)		0/124 (0%)
	Dabigatran 220 mg (DTI)		0/129 (0%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	90 days	0/317 (0%)
	Warfarin (VKA)		1/324 (0.3%)
Iliopoulos 2011 Abstract P104	Dabigatran 110 mg (DTI)	5 days	0/40 (0%)
	Tinzaparin (NA)		0/40 (0%)
	Fondaparinux (FXaI)		0/40 (0%)
	Enoxaparin (LMWH)		0/40 (0%)
Lachiewicz 2004 15568526	IPC (Venaflow) (NA)	post-operative days	0/206 (0%)
	IPC (Kendal) (NA)		1/217 (0.5%)
Lassen 2007 17868430	Warfarin (VKA)	Post-operative years	0/109 (0%)
	Enoxaparin (LMWH)		2/109 (1.8%)

Study	Arm	Timepoint	n/N (%)
Lassen 2010B 20206776	Apixaban (NA)	10-14 (during intended treatment) days	4/1528 (0.3%)
	Enoxaparin (NA)		0/1529 (0%)
	Apixaban (FXaI)	30-60 after completion of treatment (during intended treatment and follow-up) days	7/1528 (0.5%)
	Enoxaparin (LMWH)		1/1529 (0.1%)
Leclerc 1996 8607589	Warfarin (VKA)	Post-operative days	3/334 (0.9%)
	Enoxaparin (LMWH)		1/336 (0.3%)
Wilson 1992 1732265	Venous foot pump (A-V Impulse System) (Mechanical)	Post-operative days	0/28 (0%)
	Control (Placebo)		0/32 (0%)
Zou 2014 24695091	Aspirin (Antiplatelet)	4 weeks	0/110 (0%)
	Rivaroxaban (FXaI)		0/102 (0%)
	Enoxaparin (LMWH)		0/112 (0%)
Readmission, bleeding or infection (combined)			
Bonneux 2006 16387501	Fondaparinux (NA)	Post-operative days	4/55 (7.3%)
	Enoxaparin (NA)		1/55 (1.8%)
Fitzgerald 2001 11407799	Warfarin (NA)	post-operative days	0/176 (0%)
	Enoxaparin (NA)		0/173 (0%)
VTE, Symptomatic			
Bauer 2001 11794149	Fondaparinux (FXaI)	49 days	5/517 (1.0%)
	Enoxaparin (LMWH)		10/517 (1.9%)
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	0/71 (0%)
	Enoxaparin (LMWH)		1/71 (1.4%)
	FXI-ASO 200 (FXiI)		2/139 (1.4%)
Comp 2001 11263636 TKR	Enoxaparin 7-10 days (NA)	30 days	46/221 (21%)
	Enoxaparin 7-10 days+ 3 weeks (NA)		38/217 (18%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	0/88 (0%)
	Edoxaban 30 mg (NA)		0/88 (0%)
	Edoxaban 15 mg (NA)		0/92 (0%)
	Edoxaban 5 mg (NA)		1/88 (1.1%)

Study	Arm	Timepoint	n/N (%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	4/299 (1.3%)
	Enoxaparin (LMWH)		1/295 (0.3%)
Hull 1993 8413432 TKA	Tinzaparin (LMWH)	90 days	1/317 (0.3%)
	Warfarin (VKA)		1/324 (0.3%)
Jiang 2014 24931228	Aspirin (NA)	5 days	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
	Aspirin (NA)	6 weeks	0/60 (0%)
	LMWH then rivaroxaban (NA)		0/60 (0%)
Leclerc 1996 8607589	Warfarin (VKA)	180 days	1/334 (0.3%)
	Enoxaparin (LMWH)		3/336 (0.9%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	0/72 (0%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		0/67 (0%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		1/79 (1.3%)
	Enoxaparin (NA)		0/77 (0%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	1/115 (0.9%)
	TAK-442 40 BID (FXaI)		5/112 (4.5%)
	TAK-442 80 BID (NA)		3/119 (2.5%)
	TAK-442 10 (NA)		2/77 (2.6%)
	TAK-442 20 (NA)		2/86 (2.3%)
	TAK-442 80 qD (NA)		1/112 (0.9%)
	Enoxaparin (LMWH)		4/109 (3.7%)
Yilmaz 2015 25852131	Enoxaparin + electrostimulation device (The Geko) (LMWH_Mechanical)	6 days	0/15 (0%)
	Enoxaparin (LMWH)		0/15 (0%)
VTE, Total			
Büller 2015 25482425	FXI-ASO 300 (NA)	~12 days	3/71 (4.2%)
	Enoxaparin (LMWH)		22/71 (31%)
	FXI-ASO 200 (FXiI)		36/139 (26%)
Cohen 2013 23782955	Eribaxaban 1 mg (FXaI)	~10 days	23/120 (19%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin 30 mg BID (LMWH)		34/188 (18%)
	Eribaxaban 2.5 mg (NA)		16/112 (14%)
	Eribaxaban 10 mg (NA)		3/27 (11%)
	Eribaxaban 0.1 mg (NA)		13/35 (37%)
	Eribaxaban 4 mg (NA)		1/74 (1.4%)
	Eribaxaban 0.5 mg (NA)		30/104 (29%)
	Eribaxaban 0.3 mg (NA)		33/89 (37%)
Fuji 2010B 20723033	Edoxaban 60 mg (NA)	11-14 days	8/88 (9.1%)
	Edoxaban 30 mg (NA)		11/88 (13%)
	Edoxaban 15 mg (NA)		24/92 (26%)
	Edoxaban 5 mg (NA)		26/88 (30%)
Fuji 2014C 25294589	Edoxaban (FXaI)	11-14 days	22/299 (7.4%)
	Enoxaparin (LMWH)		41/295 (14%)
Fuji 2014D 22952213 TKA	Placebo (Placebo)	10-14 (during treatment period) days	38/72 (53%)
	Darexaban 15 mg BID (NA)		22/81 (27%)
	Darexaban 30 mg BID (FXaI)		11/71 (15%)
	Enoxaparin (LMWH)		15/66 (23%)
Verhamme 2011 21284801	Enoxaparin then TB-402 0.3 mg/kg (NA)	7-11 days	12/72 (17%)
	Enoxaparin then TB-402 0.6 mg/kg (NA)		16/67 (24%)
	Enoxaparin then TB-402 1.2 mg/kg (NA)		19/79 (24%)
	Enoxaparin (NA)		30/77 (39%)
Weitz 2010 20886185	TAK-442 40 qD (NA)	10 days	27/115 (23%)
	TAK-442 40 BID (FXaI)		24/112 (21%)
	TAK-442 80 BID (NA)		17/119 (14%)
	TAK-442 10 (NA)		30/77 (39%)
	TAK-442 20 (NA)		33/86 (38%)
	TAK-442 80 qD (NA)		29/112 (26%)
	Enoxaparin (LMWH)		24/109 (22%)
Yilmaz 2015 25852131	Enoxaparin + electrostimulation device (The	6 days	0/15 (0%)

Study	Arm	Timepoint	n/N (%)
	Geko) (LMWH_Mechanical)		
	Enoxaparin (LMWH)		0/15 (0%)
Wound complication			
Jiang 2014 24931228	Aspirin (NA)	5 days	1/60 (1.7%)
	LMWH then rivaroxaban (NA)		2/60 (3.3%)
Zou 2014 24695091	Aspirin (NA)	4 weeks	2/110 (1.8%)
	Rivaroxaban (NA)		5/102 (4.9%)
	Enoxaparin (NA)		3/112 (2.7%)

Table F3. RCT hip fracture surgery

Study	Arm	Timepoint	n/N (%)
Bleeding, Fatal			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	0/831 (0%)
	Enoxaparin (LMWH)		1/842 (0.1%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	8/329 (2.4%)
	Fondaparinux 25-31 days (NA)		6/327 (1.8%)
Jørgensen 1992 1314147	Placebo (Placebo)	Post-operative days	0/38 (0%)
	Dalteparin (LMWH)		0/30 (0%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar	0/488 (0%)
	Enoxaparin (NA)		0/499 (0%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	0/46 (0%)
	Heparin (UFH)		1/44 (2.3%)
Powers 1989 2650646	Placebo (Placebo)	21 days	0/63 (0%)
	Aspirin (Antiplatelet)		0/66 (0%)
	Warfarin (VKA)		0/65 (0%)
Sasaki 2011 21293896	Placebo (Placebo)	14 days	0/29 (0%)
-	Fondaparinux (FXaI)		0/27 (0%)
	Enoxaparin (LMWH)		0/28 (0%)
Bleeding, Leading to infection			
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	0/329 (0%)
	Fondaparinux 25-31 days (NA)		0/327 (0%)
Bleeding, Leading to reoperation			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	3/831 (0.4%)
	Enoxaparin (LMWH)		2/842 (0.2%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	2/329 (0.6%)
	Fondaparinux 25-31 days (NA)		2/327 (0.6%)
Bleeding, Major			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	18/831 (2.2%)

Study	Arm	Timepoint	n/N (%)
	Enoxaparin (LMWH)		19/842 (2.3%)
	Fondaparinux 6-8 days (NA)	32 days	2/329 (0.6%)
	Fondaparinux 25-31 days (NA)		8/327 (2.4%)
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	1/312 (0.3%)
	Semuloparin 8 days (NA)		0/157 (0%)
Fuji 2014B 24680549	Edoxaban (FXaI)	25-35 days	1/59 (1.7%)
	Enoxaparin (LMWH)		1/29 (3.4%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days days	5/488 (1.0%)
	Enoxaparin (NA)		3/499 (0.6%)
Powers 1989 2650646	Placebo (Placebo)	21 days	5/63 (7.9%)
	Aspirin (Antiplatelet)		1/66 (1.5%)
	Warfarin (VKA)		5/65 (7.7%)
Sasaki 2011 21293896	Placebo (Placebo)	14 days	0/29 (0%)
	Fondaparinux (FXaI)		2/27 (7.4%)
	Enoxaparin (LMWH)		0/28 (0%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	1/66 (1.5%)
	Enoxaparin (NA)		2/66 (3.0%)
Bleeding, Surgical site/joint			
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	0/329 (0%)
-	Fondaparinux 25-31 days (NA)		6/327 (1.8%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	1/66 (1.5%)
	Enoxaparin (NA)		0/66 (0%)
DVT, Proximal			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	6/650 (0.9%)
	Enoxaparin (LMWH)		28/646 (4.3%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	35/222 (16%)
	Fondaparinux 25-31 days (NA)		2/221 (0.9%)
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	4/267 (1.5%)

Study	Arm	Timepoint	n/N (%)
	Semuloparin 8 days (NA)		11/127 (8.7%)
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	0/46 (0%)
--	Enoxaparin (LMWH)		0/27 (0%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	7-11 days	13/426 (3.1%)
	Enoxaparin (NA)		26/420 (6.2%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	12/32 (38%)
	Heparin (UFH)		5/30 (17%)
Sasaki 2011 21293896	Placebo (Placebo)	14 days	4/29 (14%)
	Fondaparinux (FXaI)		1/27 (3.7%)
	Enoxaparin (LMWH)		2/28 (7.1%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	3/57 (5.3%)
	Enoxaparin (NA)		2/52 (3.8%)
DVT, Symptomatic			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	1/831 (0.1%)
	Enoxaparin (LMWH)		1/840 (0.1%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	6/330 (1.8%)
	Fondaparinux 25-31 days (NA)		1/326 (0.3%)
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	0/46 (0%)
	Enoxaparin (LMWH)		0/27 (0%)
Kennedy 2000 10697085	Aspirin (Antiplatelet)	post-operative days	4/73 (5.5%)
	VFP (AV impulse system) (Mechanical)		2/70 (2.9%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	0/57 (0%)
	Enoxaparin (NA)		0/52 (0%)
DVT, Total			
Eriksson 2001 11794148	Fondaparinux (FXaI)	11 days	49/624 (7.9%)
	Enoxaparin (LMWH)		117/623 (19%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	74/218 (34%)
	Fondaparinux 25-31 days (NA)		3/208 (1.4%)
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	9/230 (3.9%)

Study	Arm	Timepoint	n/N (%)
	Semuloparin 8 days (NA)		17/100 (17%)
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	3/46 (6.5%)
	Enoxaparin (LMWH)		1/27 (3.7%)
Jørgensen 1992 1314147	Placebo (Placebo)	Post-operative days	18/38 (47%)
	Dalteparin (LMWH)		5/30 (17%)
Kennedy 2000 10697085	Aspirin (NA)	post-operative days	7/73 (9.6%)
-	VFP (AV impulse system) (NA)		4/70 (5.7%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	7-11 days	63/379 (17%)
	Enoxaparin (NA)		79/367 (22%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	14/32 (44%)
	Heparin (UFH)		6/30 (20%)
Sasaki 2011 21293896	Placebo (Placebo)	14 days	19/29 (66%)
	Fondaparinux (FXaI)		7/27 (26%)
	Enoxaparin (LMWH)		16/28 (57%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	5/57 (8.8%)
	Enoxaparin (NA)		8/52 (15%)
Major adverse event, other			
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	6/312 (1.9%)
	Semuloparin 8 days (NA)		7/157 (4.5%)
Fuji 2014B 24680549	Edoxaban (FXaI)	25-35 days	3/59 (5.1%)
	Enoxaparin (LMWH)		3/29 (10%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	period from the first injection given during the study up to the last injection plus 3 calendar days days days	28/488 (5.7%)
	Enoxaparin (NA)		27/499 (5.4%)
Mortality, 30 day or in-hospital (AE)			
Eriksson 2001 11794148	Fondaparinux (FXaI)	49 days	38/831 (4.6%)
	Enoxaparin (LMWH)		42/842 (5.0%)
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	0/312 (0%)
-	Semuloparin 8 days (NA)		2/157 (1.3%)

Study	Arm	Timepoint	n/N (%)
Jørgensen 1992 1314147	Placebo (Placebo)	Post-operative days	4/38 (11%)
	Dalteparin (LMWH)		3/30 (10%)
Lassen 2012 22429800 HFx	Semuloparin (NA)	7-11 days	4/488 (0.8%)
	Enoxaparin (NA)		2/499 (0.4%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	2/46 (4.3%)
	Heparin (UFH)		3/44 (6.8%)
PE, Fatal			
Eriksson 2001 11794148	Fondaparinux (FXaI)	49 days	8/831 (1.0%)
	Enoxaparin (LMWH)		7/840 (0.8%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	1/330 (0.3%)
	Fondaparinux 25-31 days (NA)		0/326 (0%)
Fisher 2013 23539696	Semuloparin 28 days (NA)	28 days	0/312 (0%)
	Semuloparin 8 days (NA)		1/157 (0.6%)
F--uji 2014B 24680549	Edoxaban (FXaI)	11-14 days	0/46 (0%)
	Enoxaparin (LMWH)		0/27 (0%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	0/46 (0%)
	Heparin (UFH)		0/44 (0%)
Powers 1989 2650646	Placebo (Placebo)	21 days	0/63 (0%)
	Aspirin (Antiplatelet)		1/66 (1.5%)
	Warfarin (VKA)		0/65 (0%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	0/66 (0%)
	Enoxaparin (NA)		0/66 (0%)
PE, Symptomatic			
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	0/46 (0%)
	Enoxaparin (LMWH)		0/27 (0%)
Sasaki 2011 21293896	Placebo (Placebo)	14 days	1/29 (3.4%)
	Fondaparinux (FXaI)		0/27 (0%)
	Enoxaparin (LMWH)		0/28 (0%)
PE, Total			

Study	Arm	Timepoint	n/N (%)
Eriksson 2001 11794148	Fondaparinux (FXaI)	49 days	11/831 (1.3%)
	Enoxaparin (LMWH)		11/840 (1.3%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	3/330 (0.9%)
	Fondaparinux 25-31 days (NA)		0/326 (0%)
Kennedy 2000 10697085	Aspirin (Antiplatelet)	post-operative days	1/73 (1.4%)
	VFP (AV impulse system) (Mechanical)		0/70 (0%)
Monreal 1989 2544742	Dalteparin (LMWH)	Post-operative days	6/46 (13%)
	Heparin (UFH)		0/44 (0%)
Powers 1989 2650646	Placebo (Placebo)	21 days	2/63 (3.2%)
	Aspirin (Antiplatelet)		1/66 (1.5%)
	Warfarin (VKA)		0/65 (0%)
The TIFDED Study Group 1999 10844404	Dalteparin (NA)	Post-operative days	0/66 (0%)
	Enoxaparin (NA)		0/66 (0%)
VTE, Symptomatic			
Eriksson 2001 11794148	Fondaparinux (FXaI)	49 days	17/831 (2.0%)
	Enoxaparin (LMWH)		13/840 (1.5%)
Eriksson 2003 12796070	Fondaparinux 6-8 days (NA)	32 days	9/330 (2.7%)
	Fondaparinux 25-31 days (NA)		1/326 (0.3%)
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	0/46 (0%)
	Enoxaparin (LMWH)		0/27 (0%)
-VTE, Total			
Fuji 2014B 24680549	Edoxaban (FXaI)	11-14 days	3/46 (6.5%)
	Enoxaparin (LMWH)		1/27 (3.7%)

Table F4. NRCS total hip replacement

Study Year PMID Region	Timepoint	Arm	n/N (%)	Between Arms Comparison	Adjusted Hazard Ratio (95% CI)	Adjusted P-Value
Total Venous Thromboembolism						
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	7/376 (1.9)	Anticoagulation (mixed) >14 days vs. Anticoagulation (mixed) 1-14 days		0.33
		Anticoagulation (mixed) >21 days	6/299 (2.0)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.53
		Anticoagulation (mixed) >28 days	3/229 (1.3)	Anticoagulation (mixed) >28 days vs Anticoagulation (mixed) 1-28 days		0.18
		Anticoagulation (mixed) 1-14 days	23/747 (3.1)			
		Anticoagulation (mixed) 1-21 days	24/824 (2.9)			
		Anticoagulation (mixed) 1-28 days	27/894 (3.0)			
Pedersen 2015 25511580 Denmark	90 days	Anticoagulation (mixed) Short duration (0-6 days)	54/4804 (1.1)	Anticoagulation (mixed) Short duration (0-6 days) vs. Anticoagulation (mixed) Extended duration (>=28 days)	0.83 (0.52, 1.31)	
		Anticoagulation (mixed) Standard duration (7-27 days)	86/6362 (1.4)	Anticoagulation (mixed) Standard duration (7-27 days) vs. Anticoagulation (mixed) Extended duration (>=28 days)	0.82 (0.50, 1.33)	
		Anticoagulation (mixed) Extended duration (>=28 days)	57/5699 (1.0)			
Total Pulmonary Embolism						
Bloch 2014 24395322 UK	90 days	Dabigatran (DTI)	2/415 (0.5)			
		LMWH + aspirin (antiplatelet)	1/164 (0.6)			
		LMWH	2/185 (1.1)			
Ishibe 2011 22101618 Japan	7 days	Fondaparinux (FXaI)	0/547 (0)			
		Enoxaparin (LMWH)	0/509 (0)			
Jameson 2011 22058295 UK	90 days	LMWH	583/85642 (0.7)	LMWH vs Aspirin	0.97 (0.81, 1.17) [propensity score matched: 0.94 (0.75, 1.17)]	0.78 [0.56]
		Aspirin (antiplatelet)	156/22942 (0.7)			
Khatod 2011 22005861 U.S.	90 days	Coumadin (warfarin) + mechanical (SCD or VFP or TED hose)	20/4602 (0.4)			
		Coumadin (warfarin) +/-	26/6063 (0.4)			

Study Year PMID Region	Timepoint	Arm	n/N (%)	Between Arms Comparison	Adjusted Hazard Ratio (95% CI)	Adjusted P-Value
		mechanical (SCD or VFP or TED hose)				
		Coumadin (warfarin)	6/1461 (0.41)			
		LMWH + mechanical (SCD or VFP or TED hose)	27/6265 (0.43)			
		LMWH +/- mechanical (SCD or VFP or TED hose)	29/7202 (0.43)			
		LMWH	2/937 (0.21)			
		Aspirin (antiplatelet) + mechanical (SCD or VFP or TED hose)	3/874 (0.34)			
		Aspirin (antiplatelet) +/- mechanical (SCD or VFP or TED hose)	4/934 (0.43)			
		Aspirin (antiplatelet)	1/60 (1.67)			
		SCD or VFP (mechanical)	5/1341 (0.37)			
		Compression stockings (mechanical)	0/192 (0)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	1/376 (0.27)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		0.28
		Anticoagulation (mixed) >21 days	1/299 (0.33)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.69
		Anticoagulation (mixed) >28 days	1/229 (0.44)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		1
		Anticoagulation (mixed) 1-14 days	7/747 (0.94)			
		Anticoagulation (mixed) 1-21 days	7/824 (0.85)			
		Anticoagulation (mixed) 1-28 days	7/894 (0.78)			
Fatal Pulmonary Embolism						
Khatod 2011 22005861 U.S.	90 days	Coumadin (warfarin) + mechanical (SCD or VFP or TED hose)	0/4602 (0)			
		Coumadin (warfarin) +/- mechanical (SCD or VFP or TED hose)	0/6063 (0)			
		Coumadin (warfarin)	0/1461 (0)			
		LMWH + mechanical (SCD or VFP or TED hose)	1/6265 (0.02)			

Study Year PMID Region	Timepoint	Arm	n/N (%)	Between Arms Comparison	Adjusted Hazard Ratio (95% CI)	Adjusted P-Value
		LMWH +/- mechanical (SCD or VFP or TED hose)	1/7202 (0.01)			
		LMWH	0/937 (0)			
		Aspirin (antiplatelet) + mechanical (SCD or VFP or TED hose)	0/874 (0)			
		Aspirin (antiplatelet) +/- mechanical (SCD or VFP or TED hose)	0/934 (0)			
		Aspirin (antiplatelet)	0/60 (0)			
		SCD or VFP (mechanical)	0/1341 (0)			
		Compression stockings (mechanical)	0/192 (0)			
Total Deep Vein Thrombosis						
Bloch 2014 24395322 UK	90 days	Dabigatran (DTI)	1/415 (0.2)			
		LMWH + aspirin (antiplatelet)	0/164 (0)			
		LMWH	3/185 (1.6)			
Ishibe 2011 22101618 Japan	1 week	Fondaparinux (FXaI)	4/547 (0.7)	Fondaparinux vs Enoxaparin		NS (adjustment NR)
		Enoxaparin (LMWH)	0/509 (0)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	6/376 (1.60)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		0.65
		Anticoagulation (mixed) >21 days	5/299 (1.67)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.81
		Anticoagulation (mixed) >28 days	2/229 (0.87)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		0.28
		Anticoagulation (mixed) 1-14 days	16/747 (2.14)			
		Anticoagulation (mixed) 1-21 days	17/824 (2.06)			
		Anticoagulation (mixed) 1-28 days	20/894 (2.24)			
Symptomatic (diagnosed) DVT						
Jameson 2011 22058295 UK	90 days	LMWH	806/85642 (0.94)	LMWH vs Aspirin	0.91 (0.79, 1.06) [propensity score matched: 0.84 (0.70, 1.03)]	0.23 [0.10]

Study Year PMID Region	Timepoint	Arm	n/N (%)	Between Arms Comparison	Adjusted Hazard Ratio (95% CI)	Adjusted P-Value
		Aspirin (antiplatelet)	227/22942 (0.99)			
Major Bleeding						
Jameson 2011 22058295 UK	30 days	LMWH	620/85642 (0.72)	LMWH vs Aspirin	0.92 (0.77, 1.09) [propensity score matched: 0.95 (0.77, 1.17)]	0.34 [0.63]
		Aspirin (antiplatelet)	176/22942 (0.77)			
Pedersen 2015 25511580 Denmark	90 days	Anticoagulation (mixed) short duration (0-6 days)	51/4804 (1.1)	Anticoagulation (mixed) Short duration (0-6 days) vs Anticoagulation (mixed) Extended duration (>=28 days)	HR 1.64 (0.83, 3.21)	
		Anticoagulation (mixed) standard duration (7-27 days)	66/6362 (1.0)	Anticoagulation (mixed) Standard duration (7-27 days) vs Anticoagulation (mixed) Extended duration (>=28 days)	HR 1.24 (0.61, 2.51)	
		Anticoagulation (mixed) extended duration (>=28 days)	37/5699 (0.7)			
Vulcano 2012 22684546 U.S.	90 days	Warfarin	3/172 (1.74)			
		Aspirin (antiplatelet)	2/705 (0.28)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	1/376 (0.27)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		0.03
		Anticoagulation (mixed) >21 days	0/299 (0)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.02
		Anticoagulation (mixed) >28 days	0/229 (0)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		0.05
		Anticoagulation (mixed) 1-14 days	14/747 (1.87)			
		Anticoagulation (mixed) 1-21 days	15/824 (1.82)			
		Anticoagulation (mixed) 1-28 days	15/894 (1.68)			
Mortality, 30 day or in-hospital (AE)	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
Vulcano 2012 22684546 U.S.	30 days	Warfarin	0/172 (0)			
		Aspirin (antiplatelet)	1/705 (0.14)			
Infection, Leading to reoperation						
Jameson 2011 22058295 UK	30 days	LMWH	312/85642 (0.36)	LMWH vs Aspirin	1.15 (0.88, 1.50)	0.29
		Aspirin (antiplatelet)	71/22942 (0.31)			

Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism; LMWH = low molecular weight heparin; PMID = PubMed identifier, SCD = Sequential Compression Device; TED = Thromboembolic Deterrent; VFP = venous foot pump; PMID = PubMed identifier; DTI = direct thrombin inhibitor; FXaI = factor Xa inhibitor, NR = not reported;

Table F5. NRCS total knee replacement

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
Total Venous Thromboembolism						
Bozic 2010 19679434 US	30 days	Warfarin	2009/51923 (3.87)	Warfarin vs Aspirin	1.36 (1.02, 1.82)	
		Aspirin (antiplatelet)	110/4719 (2.33)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	8/671 (1.19)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		<0.01
		Anticoagulation (mixed) >21 days	5/532 (0.94)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		<0.01
		Anticoagulation (mixed) >28 days	3/390 (0.77)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		<0.01
		Anticoagulation (mixed) 1-14 days	62/1401 (4.43)			
		Anticoagulation (mixed) 1-21 days	65/1540 (4.22)			
		Anticoagulation (mixed) 1-28 days	67/1682 (3.98)			
Llau 2011 Abstract 6AP3-2 Spain	90 days	Enoxaparin (LMWH) (start before surgery)	0/834 (0)			
		Enoxaparin (LMWH) (start after surgery)	2/688 (0.29)			
Total Pulmonary Embolism						
Bloch 2014 24395322 UK	90 days	Dabigatran (DTI)	2/457 (0.4)			
		LMWH + aspirin (antiplatelet)	0/141 (0)			
		LMWH	1/366 (0.3)			
Jameson 2012 22733945 UK	90 days	LMWH	539/120639 (0.45)	LMWH vs Aspirin	0.88 (0.74, 1.05)	0.16
		Aspirin (antiplatelet)	178/36159 (0.49)			
Khatod 2012 21641758 U.S.	90 days	Coumadin (warfarin) + mechanical	23/7708 (0.30)			
		Coumadin (warfarin) +/- mechanical	31/9634 (0.32)			
		Coumadin (warfarin)	8/1926 (0.42)			
		LMWH + mechanical	47/9128 (0.51)			
		LMWH +/- mechanical	55/10662 (0.52)			
		LMWH	8/1534 (0.52)			

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
		Aspirin (antiplatelet) + mechanical	15/3479 (0.43)			
		Aspirin (antiplatelet) +/- mechanical	16/3777 (0.42)			
		Aspirin (antiplatelet)	1/298 (0.34)			
		SCD or VFP (mechanical)	20/2779 (0.72)			
		Compression stockings (mechanical)	1/280 (0.36)			
Llau 2011 Abstract 6AP3-2 Spain	90 days	Enoxaparin (LMWH) (start before surgery)	4/834 (0.49)			
		Enoxaparin (LMWH) (start after syrgert)	5/688 (0.74)			
Rath 2013 23566737 UK	90 days	Rivaroxaban (FXaI)	24/266 (4)			
		Aspirin (antiplatelet) +/- enoxaparin (LMWH)	2/596 (0.7)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	1/671 (0.15)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		0.01
		Anticoagulation (mixed) >21 days	0/532 (0)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.01
		Anticoagulation (mixed) >28 days	0/390 (0)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		0.03
		Anticoagulation (mixed) 1-14 days	17/1401 (1.21)			
		Anticoagulation (mixed) 1-21 days	18/1540 (1.17)			
		Anticoagulation (mixed) 1-28 days	18/1682 (1.07)			
Fatal Pulmonary Embolism						
Khatod 2012 21641758 U.S.	90 days	LMWH + mechanical	1/9128 (0.01)			
		LMWH +/- mechanical	1/10662 (0.01)			
		LMWH	0/1534 (0)			
		Coumadin (warfarin) + mechanical	1/7708 (0.01)			
		Coumadin (warfarin) +/- mechanical	1/9634 (0.01)			
		Coumadin (warfarin)	0/1926 (0)			
		Aspirin (antiplatelet) + mechanical	0/3479 (0)			

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
		Aspirin (antiplatelet) +/- mechanical	0/3777 (0)			
		Aspirin (antiplatelet)	0/298 (0)			
		SCD or VFP (mechanical)	1/2779 (0.04)			
		Compression stockings (mechanical)	0/280 (0)			
Rath 2013 23566737 UK	90 days	Rvaroxaban	0/266 (0)			
		Aspirin (antiplatelet) +/- enoxaparin (LMWH)	0/596 (0)			
Total Deep Vein Thrombosis						
Bloch 2014 24395322 UK	90 days	Dabigatran (DTI)	5/457 (1.1)			
		LMWH + aspirin (antiplatelet)	0/141 (0)			
		LMWH	7/366 (1.9)			
Jameson 2012 22733945 UK	90 days	LMWH	762/120639 (0.63)	LMWH vs Aspirin	0.93 (0.81, 1.08)	0.37
		Aspirin (antiplatelet)	239/36159 (0.66)			
Kang 2015 25963358 China	7 days	Foot pump (mechanical) + LMWH	34/332 (10.24)	foot pump + LMWH vs LMWH	0.91 (0.84, 1.01)	0.09
		LMWH	141/693 (20.35)			
Llau 2011 Abstract 6AP3-2 Spain	90 days	Enoxaparin (LMWH) (start before surgery)	8/834 (0.98)			
		Enoxaparin (LMWH) (start after surgery)	8/688 (1.19)			
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	7/671 (1.07)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		<0.01
		Anticoagulation (mixed) >21 days	5/532 (0.94)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.01
		Anticoagulation (mixed) >28 days	3/390 (0.77)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		0.01
		Anticoagulation (mixed) 1-14 days	45/1401 (3.21)			
		Anticoagulation (mixed) 1-21 days	47/1540 (3.05)			
		Anticoagulation (mixed) 1-28 days	49/1682 (2.91)			
Symptomatic Deep Vein Thrombosis						

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
Rath 2013 23566737 UK	90 days	Rivaroxaban (FXaI)	2/266 (0.75)	rivaroxaban vs aspirin +/- enoxaparin		0.23 (adjustment NR)
		Aspirin (antiplatelet) +/- enoxaparin (LMWH)	1/596 (0.17)			
Major Bleeding						
Wells 2010 21348557 U.S.	90 days	Anticoagulation (mixed) >14 days	3/671 (0.45)	Anticoagulation (mixed) >14 days vs, Anticoagulation (mixed) 1-14 days		0.03
		Anticoagulation (mixed) >21 days	2/532 (0.38)	Anticoagulation (mixed) >21 days vs. Anticoagulation (mixed) 1-21 days		0.04
		Anticoagulation (mixed) >28 days	1/390 (0.26)	Anticoagulation (mixed) >28 days vs. Anticoagulation (mixed) 1-28 days		0.07
		Anticoagulation (mixed) 1-14 days	22/1401 (1.57)			
		Anticoagulation (mixed) 1-21 days	23/1540 (1.49)			
		Anticoagulation (mixed) 1-28 days	24/1682 (1.43)			
Jameson 2012 22733945 UK	30 days	LMWH	465/120639 (0.39)	LMWH vs Aspirin	1.01 (0.83, 1.22)	0.94
		Aspirin (antiplatelet)	134/36159 (0.37)			
Surgical Site Bleeding						
Bozic 2010 19679434 US	30 days	Warfarin	548/51923 (1.06)	Warfarin vs Aspirin	0.97 (0.65, 1.47)	
		Aspirin (antiplatelet)	30/4719 (0.64)			.
Mortality, 30 day or in-hospital						
Bozic 2010 19679434 US	30 days	Warfarin	54/51923 (0.1)	Warfarin vs Aspirin	0.54 (0.25, 1.15)	
		Aspirin (antiplatelet)	9/4719 (0.19)			
Infection, Wound						
Bozic 2010 19679434 US	30 days	Warfarin	6349/51923 (12.23)	Warfarin vs Aspirin	1.10 (0.96, 1.26)	
		Aspirin (antiplatelet)	559/4719 (11.85)			
Infection, Leading to reoperation						
Jameson 2012 22733945 UK	30 days	LMWH	224/120639 (0.19)	LMWH vs Aspirin	0.73 (0.58, 0.94)	
		Aspirin (antiplatelet)	94/36159 (0.26)			
Return to OR,						

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparison	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
bleeding or infection						
Rath 2013 23566737 UK	90 days	Rivaroxaban (FXaI)	7/266 (2.6)	Rivaroxaban vs aspirin +/- enoxaparin		0.01 (adjustment NR)
		Aspirin (antiplatelet) +/- enoxaparin (LMWH)	2/596 (0.3)			

Abbreviations: DVT = deep vein thrombosis; VTE = venous thromboembolism; PE = pulmonary embolism; LMWH = low molecular weight heparin; SCD = Sequential Compression Device; TED = Thromboembolic Deterrent; VFP = venous foot pump; PMID = PubMed identifier; DTI = direct thrombin inhibitor; FXaI = factor Xa inhibitor; NR = not reported; OR = operating room

Table F6. NRCS hip fracture surgery

Study Year PMID Region	Timepoint	Arm (Class)	n/N (%)	Between Arms Comparator	Adjusted Odds Ratio (95% CI)	Adjusted P-Value
PE, Total						
Tsuda 2014 25034972 Japan	Post-operative	Mechanical + Fondaparinux (FXaI)	29/4792 (0.61)	Mechanical + fondaparinux vs Mechanical	0.67 (0.44, 0.99)	0.05
		Mechanical	160/17984 (0.89)			
PE, Fatal						
Tsuda 2014 25034972 Japan	in hospital	Mechanical + Fondaparinux (FXaI)	4/4792 (0.083)	Mechanical + fondaparinux vs Mechanical		0.53
		Mechanical	21/17984 (0.11)			

Abbreviations: PE = pulmonary embolism; PMID = PubMed identifier; FXaI = factor Xa inhibitor

Table F7.1. Network meta-analysis pairwise results: Total hip replacement, intervention class comparisons of DVT

	LMWH + Mechanical	FXaI	DTI	FEI	Mechanical	Antiplatelet	LMWH	VKA	UFH	Placebo
LMWH + Mechanical	LMWH + Mechanical	3.06 (1, 10.7)	3.45 (1.08, 12.5)	3.43 (0.582, 21.8)	4.15 (1.25, 14.6)	4.13 (1.04, 17.8)	5.09 (1.77, 16.5)	7.59 (2.37, 27.1)	7.92 (2.59, 27.4)	11.9 (3.98, 39.9)
FXaI	0.327 (0.0938, 0.999)	FXaI	1.13 (0.583, 2.14)	1.11 (0.281, 4.38)	1.35 (0.672, 2.61)	1.34 (0.49, 3.53)	1.66 (1.11, 2.44)	2.48 (1.28, 4.64)	2.58 (1.5, 4.47)	3.86 (2.37, 6.32)
DTI	0.289 (0.0801, 0.927)	0.888 (0.466, 1.72)	DTI	0.989 (0.216, 4.64)	1.2 (0.563, 2.47)	1.19 (0.418, 3.37)	1.48 (0.879, 2.48)	2.2 (1.06, 4.51)	2.29 (1.33, 4.03)	3.42 (1.86, 6.45)
FEI	0.291 (0.0458, 1.72)	0.899 (0.228, 3.55)	1.01 (0.216, 4.62)	FEI	1.21 (0.259, 5.49)	1.21 (0.217, 6.45)	1.49 (0.353, 6.26)	2.23 (0.477, 10.1)	2.32 (0.527, 10.2)	3.47 (0.808, 15.1)
Mechanical	0.241 (0.0685, 0.802)	0.743 (0.384, 1.49)	0.835 (0.405, 1.78)	0.826 (0.182, 3.86)	Mechanical	1 (0.367, 2.72)	1.23 (0.72, 2.17)	1.84 (1.03, 3.35)	1.92 (1.04, 3.71)	2.87 (1.56, 5.46)
Antiplatelet	0.242 (0.0561, 0.965)	0.744 (0.283, 2.04)	0.838 (0.297, 2.39)	0.826 (0.155, 4.6)	1 (0.368, 2.73)	Antiplatelet	1.24 (0.501, 3.11)	1.84 (0.752, 4.63)	1.92 (0.729, 5.23)	2.87 (1.19, 7.3)
LMWH	0.196 (0.0608, 0.566)	0.601 (0.409, 0.9)	0.677 (0.403, 1.14)	0.671 (0.16, 2.83)	0.81 (0.461, 1.39)	0.808 (0.321, 2)	LMWH	1.49 (0.883, 2.5)	1.55 (1.07, 2.31)	2.32 (1.65, 3.35)
VKA	0.132 (0.0369, 0.422)	0.404 (0.215, 0.78)	0.455 (0.222, 0.941)	0.448 (0.099, 2.1)	0.544 (0.299, 0.968)	0.542 (0.216, 1.33)	0.67 (0.4, 1.13)	VKA	1.04 (0.565, 1.98)	1.56 (0.864, 2.91)
UFH	0.126 (0.0365, 0.386)	0.387 (0.224, 0.669)	0.437 (0.248, 0.75)	0.431 (0.098, 1.9)	0.522 (0.27, 0.962)	0.521 (0.191, 1.37)	0.644 (0.434, 0.934)	0.961 (0.504, 1.77)	UFH	1.5 (0.905, 2.48)
Placebo	0.0843 (0.0251, 0.251)	0.259 (0.158, 0.423)	0.292 (0.155, 0.538)	0.288 (0.0664, 1.24)	0.349 (0.183, 0.642)	0.348 (0.137, 0.843)	0.431 (0.298, 0.608)	0.641 (0.344, 1.16)	0.669 (0.404, 1.11)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Table F7.2. Network meta-analysis pairwise results: Total hip replacement, specific intervention comparisons of DVT

	Enoxaparin+ IPC	Apixaban	Edoxaban	Enoxaparin+ GCS	Desirudin	Semuloparin	Fondaparinux	Darexaban	VFP	Dabigatran
Enoxaparin+ IPC	Enoxaparin+ IPC	5.88 (0.467, 231)	7.4 (0.553, 296)	7.77 (0.892, 261)	10.7 (0.996, 394)	10.3 (0.857, 411)	12.5 (1.18, 473)	13.1 (1.14, 509)	13.4 (1.2, 500)	16.6 (1.49, 618)
Apixaban	0.17 (0.004, 2.14)	Apixaban	1.24 (0.282, 5.37)	1.35 (0.281, 6.45)	1.83 (0.584, 5.91)	1.77 (0.464, 6.79)	2.12 (0.709, 7.13)	2.23 (0.629, 8.24)	2.28 (0.673, 7.68)	2.82 (0.847, 9.43)
Edoxaban	0.135 (0.003, 1.81)	0.806 (0.186, 3.54)	Edoxaban	1.09 (0.206, 5.61)	1.48 (0.43, 5.27)	1.41 (0.336, 6.01)	1.72 (0.507, 6.28)	1.8 (0.459, 7.29)	1.83 (0.493, 6.83)	2.27 (0.63, 8.46)
Enoxaparin+ GCS	0.129 (0.004, 1.12)	0.741 (0.155, 3.56)	0.916 (0.178, 4.84)	Enoxaparin+ GCS	1.35 (0.355, 5.4)	1.3 (0.287, 6.05)	1.58 (0.421, 6.43)	1.66 (0.388, 7.37)	1.68 (0.414, 6.97)	2.09 (0.519, 8.7)
Desirudin	0.0936 (0.00254, 1)	0.546 (0.169, 1.71)	0.675 (0.19, 2.32)	0.741 (0.185, 2.81)	Desirudin	0.959 (0.314, 2.87)	1.15 (0.513, 2.84)	1.22 (0.443, 3.41)	1.24 (0.501, 3.03)	1.54 (0.613, 3.88)
Semuloparin	0.0972 (0.002, 1.17)	0.566 (0.147, 2.15)	0.707 (0.166, 2.98)	0.772 (0.165, 3.49)	1.04 (0.348, 3.19)	Semuloparin	1.2 (0.422, 3.91)	1.27 (0.376, 4.45)	1.3 (0.396, 4.1)	1.61 (0.502, 5.13)
Fondaparinux	0.0799 (0.002, 0.847)	0.471 (0.14, 1.41)	0.582 (0.159, 1.97)	0.634 (0.155, 2.37)	0.867 (0.352, 1.95)	0.832 (0.256, 2.37)	Fondaparinux	1.05 (0.372, 2.82)	1.07 (0.402, 2.58)	1.34 (0.502, 3.22)
Darexaban	0.0764 (0.002, 0.873)	0.448 (0.121, 1.59)	0.556 (0.137, 2.18)	0.603 (0.136, 2.58)	0.821 (0.293, 2.26)	0.789 (0.225, 2.66)	0.957 (0.354, 2.69)	Darexaban	1.02 (0.336, 2.96)	1.27 (0.423, 3.67)
VFP	0.0745 (0.002, 0.833)	0.439 (0.13, 1.49)	0.545 (0.146, 2.03)	0.594 (0.143, 2.42)	0.806 (0.331, 2)	0.77 (0.244, 2.52)	0.934 (0.387, 2.49)	0.98 (0.338, 2.98)	VFP	1.24 (0.468, 3.36)
Dabigatran	0.0601 (0.002, 0.67)	0.355 (0.106, 1.18)	0.44 (0.118, 1.59)	0.479 (0.115, 1.93)	0.65 (0.258, 1.63)	0.623 (0.195, 1.99)	0.748 (0.311, 1.99)	0.789 (0.272, 2.37)	0.806 (0.297, 2.14)	Dabigatran
Aspirin	0.0574 (0.001, 0.67)	0.334 (0.0892, 1.25)	0.417 (0.101, 1.7)	0.455 (0.101, 2.01)	0.615 (0.22, 1.77)	0.589 (0.166, 2.13)	0.714 (0.262, 2.18)	0.751 (0.233, 2.53)	0.765 (0.251, 2.31)	0.946 (0.312, 2.95)
Dalteparin	0.0544 (0.001, 0.574)	0.322 (0.0947, 1)	0.399 (0.109, 1.35)	0.433 (0.106, 1.62)	0.59 (0.252, 1.28)	0.566 (0.176, 1.66)	0.684 (0.288, 1.61)	0.713 (0.254, 1.93)	0.729 (0.285, 1.74)	0.908 (0.343, 2.23)
Enoxaparin	0.0526 (0.001, 0.519)	0.306 (0.114, 0.813)	0.38 (0.124, 1.11)	0.416 (0.119, 1.38)	0.56 (0.307, 1.04)	0.538 (0.211, 1.36)	0.648 (0.371, 1.24)	0.684 (0.302, 1.57)	0.696 (0.339, 1.42)	0.864 (0.432, 1.72)
IPC	0.05 (0.001, 0.563)	0.292 (0.0838, 1.01)	0.364 (0.0931, 1.38)	0.396 (0.0915, 1.64)	0.535 (0.207, 1.4)	0.514 (0.154, 1.72)	0.624 (0.242, 1.72)	0.654 (0.217, 2.01)	0.664 (0.238, 1.83)	0.824 (0.298, 2.33)
Rivaroxaban	0.0402 (0.001, 0.454)	0.238 (0.0665, 0.836)	0.294 (0.0762, 1.14)	0.321 (0.0739, 1.35)	0.436 (0.16, 1.17)	0.418 (0.121, 1.4)	0.504 (0.192, 1.41)	0.531 (0.172, 1.66)	0.54 (0.184, 1.53)	0.67 (0.232, 1.95)
TB402	0.0355 (0.001, 0.559)	0.211 (0.0352, 1.27)	0.262 (0.0409, 1.68)	0.285 (0.0417, 1.93)	0.389 (0.0783, 1.94)	0.373 (0.0634, 2.16)	0.452 (0.0924, 2.36)	0.473 (0.0883, 2.59)	0.482 (0.091, 2.46)	0.597 (0.113, 3.15)
Heparin	0.0364 (0.001, 0.36)	0.213 (0.0708, 0.593)	0.264 (0.0794, 0.815)	0.288 (0.0775, 0.991)	0.39 (0.212, 0.678)	0.375 (0.132, 0.989)	0.451 (0.227, 0.932)	0.474 (0.19, 1.16)	0.483 (0.223, 0.984)	0.6 (0.266, 1.29)
Tinzaparin	0.0355 (0.001, 0.369)	0.208 (0.0627, 0.625)	0.256 (0.0714, 0.854)	0.279 (0.0711, 1.04)	0.38 (0.161, 0.844)	0.365 (0.116, 1.05)	0.44 (0.195, 1.02)	0.461 (0.169, 1.22)	0.472 (0.184, 1.12)	0.585 (0.228, 1.4)
Warfarin	0.03 (0.001, 0.322)	0.177 (0.0534, 0.552)	0.219 (0.06, 0.758)	0.239 (0.0593, 0.89)	0.324 (0.137, 0.738)	0.311 (0.0979, 0.923)	0.376 (0.16, 0.907)	0.394 (0.141, 1.08)	0.401 (0.157, 0.976)	0.498 (0.191, 1.24)
Placebo	0.0217 (0.001, 0.216)	0.127 (0.0434, 0.353)	0.157 (0.0478, 0.484)	0.171 (0.0478, 0.579)	0.232 (0.114, 0.455)	0.223 (0.0795, 0.589)	0.269 (0.139, 0.542)	0.282 (0.119, 0.66)	0.287 (0.132, 0.596)	0.358 (0.159, 0.77)

	Aspirin	Dalteparin	Enoxaparin	IPC	Rivaroxaban	TB402	Heparin	Tinzaparin	Warfarin	Placebo
Enoxaparin+ IPC	17.4 (1.49, 672)	18.4 (1.74, 687)	19 (1.93, 674)	20 (1.78, 790)	24.9 (2.2, 935)	28.2 (1.79, 1.3e+03)	27.5 (2.78, 1e+03)	28.2 (2.71, 1.05e+03)	33.3 (3.11, 1.27e+03)	46.1 (4.64, 1.66e+03)
Apixaban	2.99 (0.801, 11.2)	3.11 (1, 10.6)	3.27 (1.23, 8.76)	3.42 (0.989, 11.9)	4.21 (1.2, 15)	4.73 (0.785, 28.4)	4.7 (1.69, 14.1)	4.82 (1.6, 16)	5.66 (1.81, 18.7)	7.89 (2.83, 23.1)
Edoxaban	2.4 (0.588, 9.87)	2.51 (0.742, 9.2)	2.63 (0.898, 8.06)	2.74 (0.727, 10.7)	3.4 (0.877, 13.1)	3.81 (0.597, 24.5)	3.79 (1.23, 12.6)	3.91 (1.17, 14)	4.57 (1.32, 16.7)	6.39 (2.07, 20.9)
Enoxaparin+ GCS	2.2 (0.498, 9.87)	2.31 (0.617, 9.42)	2.41 (0.724, 8.43)	2.53 (0.61, 10.9)	3.12 (0.742, 13.5)	3.51 (0.519, 24)	3.48 (1.01, 12.9)	3.59 (0.965, 14.1)	4.19 (1.12, 16.9)	5.84 (1.73, 20.9)
Desirudin	1.63 (0.566, 4.54)	1.69 (0.782, 3.97)	1.78 (0.963, 3.25)	1.87 (0.713, 4.83)	2.29 (0.853, 6.25)	2.57 (0.516, 12.8)	2.56 (1.48, 4.71)	2.63 (1.18, 6.21)	3.09 (1.36, 7.31)	4.3 (2.2, 8.76)
Semuloparin	1.7 (0.47, 6.01)	1.77 (0.602, 5.69)	1.86 (0.738, 4.74)	1.94 (0.58, 6.5)	2.39 (0.713, 8.27)	2.68 (0.463, 15.8)	2.67 (1.01, 7.57)	2.74 (0.952, 8.6)	3.21 (1.08, 10.2)	4.48 (1.7, 12.6)
Fondaparinux	1.4 (0.458, 3.82)	1.46 (0.621, 3.48)	1.54 (0.804, 2.7)	1.6 (0.58, 4.13)	1.98 (0.711, 5.21)	2.21 (0.424, 10.8)	2.22 (1.07, 4.4)	2.27 (0.981, 5.13)	2.66 (1.1, 6.27)	3.72 (1.85, 7.17)
Darexaban	1.33 (0.395, 4.3)	1.4 (0.518, 3.94)	1.46 (0.638, 3.31)	1.53 (0.496, 4.62)	1.88 (0.602, 5.82)	2.11 (0.387, 11.3)	2.11 (0.865, 5.26)	2.17 (0.823, 5.9)	2.54 (0.926, 7.07)	3.54 (1.51, 8.38)
VFP	1.31 (0.434, 3.99)	1.37 (0.574, 3.51)	1.44 (0.707, 2.95)	1.51 (0.547, 4.19)	1.85 (0.652, 5.42)	2.07 (0.406, 11)	2.07 (1.02, 4.49)	2.12 (0.895, 5.43)	2.5 (1.02, 6.38)	3.48 (1.68, 7.59)
Dabigatran	1.06 (0.339, 3.2)	1.1 (0.448, 2.92)	1.16 (0.58, 2.32)	1.21 (0.429, 3.35)	1.49 (0.514, 4.32)	1.68 (0.318, 8.85)	1.67 (0.777, 3.76)	1.71 (0.713, 4.38)	2.01 (0.803, 5.23)	2.8 (1.3, 6.27)
Aspirin	Aspirin	1.05 (0.422, 2.84)	1.09 (0.458, 2.69)	1.15 (0.415, 3.16)	1.41 (0.449, 4.61)	1.59 (0.29, 8.91)	1.58 (0.644, 4.14)	1.62 (0.646, 4.35)	1.9 (0.828, 4.54)	2.65 (1.17, 6.43)
Dalteparin	0.957 (0.353, 2.37)	Dalteparin	1.05 (0.543, 1.91)	1.1 (0.467, 2.37)	1.35 (0.482, 3.53)	1.52 (0.291, 7.38)	1.51 (0.813, 2.74)	1.55 (0.745, 3.23)	1.82 (0.998, 3.2)	2.53 (1.33, 4.71)
Enoxaparin	0.913 (0.372, 2.18)	0.952 (0.525, 1.84)	Enoxaparin	1.04 (0.482, 2.25)	1.29 (0.581, 2.85)	1.45 (0.32, 6.42)	1.44 (0.998, 2.17)	1.48 (0.844, 2.76)	1.73 (0.94, 3.33)	2.42 (1.7, 3.56)
IPC	0.873 (0.316, 2.41)	0.911 (0.422, 2.14)	0.958 (0.445, 2.07)	IPC	1.23 (0.418, 3.72)	1.38 (0.26, 7.46)	1.38 (0.62, 3.19)	1.41 (0.627, 3.38)	1.66 (0.902, 3.19)	2.31 (1.06, 5.21)
Rivaroxaban	0.709 (0.217, 2.23)	0.739 (0.283, 2.07)	0.775 (0.35, 1.72)	0.812 (0.269, 2.39)	Rivaroxaban	1.12 (0.316, 3.98)	1.12 (0.473, 2.74)	1.15 (0.448, 3.07)	1.35 (0.499, 3.75)	1.87 (0.838, 4.37)
TB402	0.631 (0.112, 3.45)	0.66 (0.136, 3.44)	0.692 (0.156, 3.13)	0.726 (0.134, 3.85)	0.893 (0.252, 3.17)	TB402	0.999 (0.219, 4.76)	1.03 (0.213, 5.14)	1.2 (0.243, 6.2)	1.68 (0.377, 7.79)
Heparin	0.634 (0.242, 1.55)	0.661 (0.365, 1.23)	0.694 (0.461, 1)	0.726 (0.314, 1.61)	0.894 (0.366, 2.12)	1 (0.21, 4.57)	Heparin	1.03 (0.531, 2.01)	1.21 (0.615, 2.35)	1.68 (1.03, 2.72)
Tinzaparin	0.617 (0.23, 1.55)	0.644 (0.31, 1.34)	0.677 (0.363, 1.18)	0.708 (0.296, 1.59)	0.872 (0.325, 2.23)	0.975 (0.195, 4.69)	0.974 (0.498, 1.88)	Tinzaparin	1.17 (0.603, 2.25)	1.64 (0.918, 2.87)
Warfarin	0.525 (0.22, 1.21)	0.55 (0.312, 1)	0.578 (0.3, 1.06)	0.603 (0.313, 1.11)	0.742 (0.267, 2)	0.831 (0.161, 4.11)	0.829 (0.426, 1.63)	0.853 (0.444, 1.66)	Warfarin	1.4 (0.741, 2.63)
Placebo	0.378 (0.155, 0.854)	0.395 (0.212, 0.755)	0.413 (0.281, 0.59)	0.432 (0.192, 0.946)	0.534 (0.229, 1.19)	0.597 (0.128, 2.65)	0.596 (0.367, 0.972)	0.611 (0.349, 1.09)	0.717 (0.381, 1.35)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that

estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, THR = total hip replacement, VFP = venous foot pump.

Table F7.3. Network meta-analysis pairwise results: Total hip replacement, intervention class comparisons of major bleeding

	Mechanical	Antiplatelet	VKA	Placebo	LMWH	DTI	FXaI	UFH	FEI
Mechanical	Mechanical	<0.01 (<0.01, >100)	>100 (11, >100)	>100 (14.5, >100)	>100 (21.6, >100)	>100 (27.4, >100)	>100 (29.5, >100)	>100 (48, >100)	>100 (>100, >100)
Antiplatelet	>100 (<0.01, >100)	Antiplatelet	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (>100, >100)
VKA	<0.01 (<0.01, 0.091)	<0.01 (<0.01, >100)	VKA	1.57 (0.43, 5.21)	**1.96 (1.1, 3.68)**	**2.54 (1.25, 5.44)**	**2.65 (1.31, 5.4)**	**4.27 (1.92, 10.1)**	>100 (>100, >100)
Placebo	<0.01 (<0.01, 0.0688)	<0.01 (<0.01, >100)	0.637 (0.192, 2.32)	Placebo	1.26 (0.451, 4.09)	1.63 (0.538, 5.63)	1.7 (0.576, 5.48)	2.77 (0.832, 9.79)	>100 (>100, >100)
LMWH	<0.01 (<0.01, 0.0463)	<0.01 (<0.01, >100)	**0.509 (0.272, 0.906)**	0.793 (0.244, 2.22)	LMWH	1.29 (0.841, 2.01)	1.34 (0.93, 1.91)	**2.18 (1.22, 3.91)**	>100 (>100, >100)
DTI	<0.01 (<0.01, 0.0365)	<0.01 (<0.01, >100)	**0.393 (0.184, 0.799)**	0.613 (0.178, 1.86)	0.775 (0.498, 1.19)	DTI	1.04 (0.585, 1.8)	1.69 (0.808, 3.42)	>100 (91, >100)
FXaI	<0.01 (<0.01, 0.0339)	<0.01 (<0.01, >100)	**0.377 (0.185, 0.761)**	0.589 (0.182, 1.74)	0.744 (0.524, 1.08)	0.96 (0.555, 1.71)	FXaI	1.63 (0.815, 3.24)	>100 (>100 , >100)
UFH	<0.01 (<0.01, 0.0208)	<0.01 (<0.01, >100)	**0.234 (0.0991, 0.522)**	0.361 (0.102, 1.2)	**0.459 (0.256, 0.82)**	0.593 (0.292, 1.24)	0.615 (0.309, 1.23)	UFH	>100 (49, >100)
FEI	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, 0.011)	<0.01 (<0.01, 0.0117)	<0.01 (<0.01, 0.0204)	FEI

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DTI = direct thrombin inhibitor, FEI = factor VIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, THR = total hip replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Table F7.4. Network meta-analysis pairwise results: Total hip replacement, specific intervention comparisons of major bleeding

	IPC	Semuloparin	Warfarin	Dalteparin	Tinzaparin	Edoxaban	Placebo	Enoxaparin	Darexaban
IPC	IPC	>100 (11.2, >100)	>100 (15, >100)	>100 (21, >100)	>100 (26.5, >100)	>100 (27.9, >100)	>100 (31.4, >100)	>100 (47.1, >100)	>100 (19.9, >100)
Semuloparin	<0.01 (<0.01, 0.0892)	Semuloparin	1.33 (0.26, 7.41)	2.07 (0.288, 14.8)	2.32 (0.39, 14.8)	2.47 (0.342, 20.2)	2.85 (0.504, 18)	3.79 (1.07, 16.1)	3.93 (0.0826, 224)
Warfarin	<0.01 (<0.01, 0.0667)	0.754 (0.135, 3.84)	Warfarin	1.53 (0.519, 4.69)	1.74 (0.6, 5.04)	1.83 (0.326, 11.1)	2.15 (0.462, 9.82)	2.81 (1.13, 8.15)	2.85 (0.0721, 154)
Dalteparin	<0.01 (<0.01, 0.0475)	0.483 (0.0677, 3.47)	0.654 (0.213, 1.93)	Dalteparin	1.11 (0.247, 5.24)	1.19 (0.172, 9.14)	1.38 (0.217, 8.85)	1.85 (0.451, 8.35)	1.86 (0.0404, 110)
Tinzaparin	<0.01 (<0.01, 0.0377)	0.43 (0.0677, 2.57)	0.576 (0.198, 1.67)	0.898 (0.191, 4.06)	Tinzaparin	1.06 (0.16, 7.9)	1.24 (0.226, 6.71)	1.64 (0.499, 5.94)	1.63 (0.0387, 88.7)
Edoxaban	<0.01 (<0.01, 0.0358)	0.404 (0.0495, 2.92)	0.546 (0.0901, 3.07)	0.841 (0.109, 5.82)	0.947 (0.127, 6.24)	Edoxaban	1.19 (0.17, 7.65)	1.52 (0.347, 7.08)	1.57 (0.0327, 79.8)
Placebo	<0.01 (<0.01, 0.0319)	0.35 (0.0556, 1.98)	0.466 (0.102, 2.16)	0.722 (0.113, 4.62)	0.806 (0.149, 4.43)	0.843 (0.131, 5.88)	Placebo	1.33 (0.436, 4.4)	1.33 (0.0358, 68.7)
Enoxaparin	<0.01 (<0.01, 0.0212)	0.264 (0.062, 0.932)	0.356 (0.123, 0.884)	0.541 (0.12, 2.22)	0.609 (0.168, 2)	0.656 (0.141, 2.88)	0.75 (0.227, 2.29)	Enoxaparin	0.987 (0.0277, 44)
Darexaban	<0.01 (<0.01, 0.0503)	0.254 (0.00447, 12.1)	0.35 (0.00651, 13.9)	0.538 (0.00906, 24.8)	0.615 (0.0113, 25.8)	0.638 (0.0125, 30.6)	0.749 (0.0146, 28)	1.01 (0.0227, 36.1)	Darexaban
Desirudin	<0.01 (<0.01, 0.0225)	0.266 (0.0475, 1.3)	0.359 (0.0853, 1.29)	0.554 (0.091, 2.87)	0.619 (0.124, 2.73)	0.66 (0.11, 3.87)	0.758 (0.168, 3.27)	1.01 (0.396, 2.58)	1 (0.0247, 50.2)
Rivaroxaban	<0.01 (<0.01, 0.0208)	0.234 (0.0399, 1.22)	0.319 (0.0721, 1.24)	0.487 (0.0795, 2.72)	0.557 (0.105, 2.61)	0.587 (0.0947, 3.55)	0.674 (0.172, 2.54)	0.901 (0.321, 2.53)	0.888 (0.0227, 45.8)
Apixaban	<0.01 (<0.01, 0.0181)	0.215 (0.0374, 1.04)	0.289 (0.0692, 1.05)	0.444 (0.0741, 2.33)	0.501 (0.0988, 2.25)	0.525 (0.0919, 3.14)	0.614 (0.132, 2.62)	0.82 (0.316, 2.1)	0.82 (0.0217, 40.5)
Dabigatran	<0.01 (<0.01, 0.015)	0.179 (0.0368, 0.731)	0.242 (0.0691, 0.718)	0.371 (0.0712, 1.68)	0.416 (0.0991, 1.55)	0.446 (0.0869, 2.2)	0.511 (0.13, 1.85)	0.685 (0.364, 1.24)	0.698 (0.0182, 32.5)
Fondaparinux	<0.01 (<0.01, 0.0136)	0.164 (0.0329, 0.682)	0.221 (0.0633, 0.666)	0.337 (0.0656, 1.55)	0.382 (0.0893, 1.43)	0.408 (0.0789, 2.07)	0.468 (0.117, 1.72)	0.623 (0.321, 1.18)	0.624 (0.0163, 29.7)
Heparin	<0.01 (<0.01, 0.011)	0.125 (0.0257, 0.529)	0.167 (0.0488, 0.524)	0.254 (0.0519, 1.23)	0.287 (0.0693, 1.15)	0.307 (0.0579, 1.65)	0.355 (0.0926, 1.33)	0.471 (0.247, 0.965)	0.472 (0.0122, 22.8)
Aspirin	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
TB402	<0.01 (<0.01, <0.01)	<0.01 (<0.01, 0.0117)	<0.01 (<0.01, 0.0153)	<0.01 (<0.01, 0.0259)	<0.01 (<0.01, 0.0269)	<0.01 (<0.01, 0.0307)	<0.01 (<0.01, 0.0327)	<0.01 (<0.01, 0.0391)	<0.01 (<0.01, 0.0689)

	Desirudin	Rivaroxaban	Apixaban	Dabigatran	Fondaparinux	Heparin	Aspirin	TB402
IPC	>100 (44.5, >100)	>100 (48, >100)	>100 (55.3, >100)	>100 (66.6, >100)	>100 (73.3, >100)	>100 (90.6, >100)	>100 (<0.01, >100)	>100 (>100, >100)
Semuloparin	3.76 (0.77, 21.1)	4.27 (0.816, 25.1)	4.65 (0.96, 26.8)	**5.59 (1.37, 27.2)**	**6.09 (1.47, 30.4)**	**7.99 (1.89, 38.9)**	>100 (<0.01, >100)	>100 (85.7, >100)
Warfarin	2.78 (0.774, 11.7)	3.13 (0.805, 13.9)	3.46 (0.955, 14.4)	**4.13 (1.39, 14.5)**	**4.52 (1.5, 15.8)**	**5.99 (1.91, 20.5)**	>100 (<0.01, >100)	>100 (65.4, >100)
Dalteparin	1.8 (0.348, 11)	2.05 (0.368, 12.6)	2.25 (0.43, 13.5)	2.7 (0.594, 14)	2.97 (0.644, 15.2)	3.93 (0.811, 19.3)	>100 (<0.01, >100)	>100 (38.6, >100)
Tinzaparin	1.62 (0.366, 8.07)	1.8 (0.383, 9.55)	2 (0.445, 10.1)	2.41 (0.644, 10.1)	2.62 (0.698, 11.2)	3.48 (0.873, 14.4)	>100 (<0.01, >100)	>100 (37.1, >100)
Edoxaban	1.52 (0.259, 9.08)	1.7 (0.281, 10.6)	1.9 (0.319, 10.9)	2.24 (0.454, 11.5)	2.45 (0.483, 12.7)	3.25 (0.607, 17.3)	>100 (<0.01, >100)	>100 (32.5, >100)
Placebo	1.32 (0.306, 5.96)	1.48 (0.394, 5.8)	1.63 (0.381, 7.58)	1.96 (0.542, 7.69)	2.13 (0.581, 8.56)	2.82 (0.753, 10.8)	>100 (<0.01, >100)	>100 (30.5, >100)
Enoxaparin	0.99 (0.387, 2.52)	1.11 (0.395, 3.11)	1.22 (0.476, 3.17)	1.46 (0.806, 2.75)	1.6 (0.849, 3.11)	**2.12 (1.04, 4.04)**	>100 (<0.01, >100)	>100 (25.6, >100)
Darexaban	0.996 (0.0199, 40.5)	1.13 (0.0218, 44)	1.22 (0.0247, 46.1)	1.43 (0.0308, 55)	1.6 (0.0336, 61.2)	2.12 (0.0439, 81.7)	>100 (<0.01, >100)	>100 (14.5, >100)
Desirudin	Desirudin	1.13 (0.273, 4.51)	1.23 (0.327, 4.68)	1.48 (0.484, 4.59)	1.61 (0.519, 5.1)	2.15 (0.64, 6.5)	>100 (<0.01, >100)	>100 (24.6, >100)
Rivaroxaban	0.888 (0.221, 3.67)	Rivaroxaban	1.1 (0.268, 4.5)	1.32 (0.396, 4.41)	1.44 (0.429, 4.97)	1.91 (0.543, 6.41)	>100 (<0.01, >100)	>100 (21.9, >100)
Apixaban	0.81 (0.214, 3.06)	0.905 (0.222, 3.73)	Apixaban	1.19 (0.394, 3.76)	1.31 (0.421, 4.08)	1.74 (0.518, 5.22)	>100 (<0.01, >100)	>100 (19.1, >100)
Dabigatran	0.676 (0.218, 2.07)	0.757 (0.227, 2.53)	0.838 (0.266, 2.54)	Dabigatran	1.1 (0.444, 2.65)	1.45 (0.551, 3.44)	>100 (<0.01, >100)	>100 (16.8, >100)
Fondaparinux	0.62 (0.196, 1.93)	0.693 (0.201, 2.33)	0.765 (0.245, 2.38)	0.911 (0.378, 2.25)	Fondaparinux	1.33 (0.492, 3.13)	>100 (<0.01, >100)	>100 (15.5, >100)
Heparin	0.465 (0.154, 1.56)	0.524 (0.156, 1.84)	0.574 (0.191, 1.93)	0.688 (0.291, 1.82)	0.752 (0.319, 2.03)	Heparin	>100 (<0.01, >100)	>100 (12.1, >100)
Aspirin	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	Aspirin	<0.01 (<0.01, >100)
TB402	<0.01 (<0.01, 0.0407)	<0.01 (<0.01, 0.0456)	<0.01 (<0.01, 0.0522)	<0.01 (<0.01, 0.0596)	<0.01 (<0.01, 0.0647)	<0.01 (<0.01, 0.0828)	>100 (<0.01, >100)	TB402

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: IPC = intermittent pneumatic compression, THR = total hip replacement.

Table F7.5. Network meta-analysis pairwise results: Total knee replacement, intervention class comparisons of DVT

	LMWH+Mechanical	FXaI	Antiplatelet+Mechanical	DTI	FXIi	LMWH
LMWH+Mechanical	LMWH+Mechanical	1.14 (0.495, 2.54)	1.15 (0.598, 2.27)	1.37 (0.514, 3.47)	1.88 (0.661, 5.45)	2.4 (1.09, 5.32)
FXaI	0.88 (0.393, 2.02)	FXaI	1.02 (0.439, 2.34)	1.21 (0.684, 2.07)	1.68 (0.804, 3.51)	2.12 (1.7, 2.71)
Antiplatelet+Mechanical	0.872 (0.441, 1.67)	0.981 (0.428, 2.28)	Antiplatelet+Mechanical	1.18 (0.447, 3.12)	1.64 (0.559, 5)	2.08 (0.925, 4.8)
DTI	0.732 (0.288, 1.95)	0.829 (0.483, 1.46)	0.845 (0.321, 2.24)	DTI	1.39 (0.586, 3.36)	1.76 (1.07, 3.03)
FXIi	0.533 (0.184, 1.51)	0.597 (0.285, 1.24)	0.61 (0.2, 1.79)	0.721 (0.298, 1.71)	FXIi	1.27 (0.63, 2.55)
LMWH	0.417 (0.188, 0.92)	0.473 (0.37, 0.587)	0.48 (0.208, 1.08)	0.568 (0.33, 0.938)	0.788 (0.393, 1.59)	LMWH
FXaI+Mechanical	0.417 (0.123, 1.46)	0.476 (0.188, 1.14)	0.479 (0.137, 1.68)	0.566 (0.196, 1.64)	0.792 (0.239, 2.55)	1.01 (0.394, 2.53)
Mechanical	0.393 (0.161, 0.977)	0.446 (0.261, 0.747)	0.456 (0.18, 1.12)	0.534 (0.269, 1.08)	0.742 (0.321, 1.76)	0.945 (0.584, 1.53)
UFH	0.281 (0.118, 0.686)	0.32 (0.197, 0.504)	0.326 (0.128, 0.8)	0.386 (0.194, 0.728)	0.531 (0.24, 1.2)	0.677 (0.448, 1.02)
VKA	0.229 (0.101, 0.53)	0.261 (0.18, 0.361)	0.263 (0.112, 0.612)	0.312 (0.17, 0.549)	0.435 (0.206, 0.909)	0.553 (0.421, 0.709)
Antiplatelet	0.203 (0.0898, 0.463)	0.231 (0.14, 0.37)	0.234 (0.105, 0.506)	0.276 (0.138, 0.534)	0.383 (0.167, 0.877)	0.488 (0.313, 0.752)
Placebo	0.14 (0.0583, 0.324)	0.157 (0.109, 0.224)	0.161 (0.065, 0.382)	0.19 (0.112, 0.31)	0.262 (0.123, 0.573)	0.334 (0.241, 0.464)

	FXaI+Mechanical	Mechanical	UFH	VKA	Antiplatelet	Placebo
LMWH+Mechanical	2.4 (0.686, 8.15)	2.55 (1.02, 6.22)	3.56 (1.46, 8.5)	4.36 (1.89, 9.94)	4.94 (2.16, 11.1)	7.17 (3.09, 17.2)
FXaI	2.1 (0.874, 5.31)	2.24 (1.34, 3.83)	3.13 (1.98, 5.06)	3.83 (2.77, 5.55)	4.34 (2.71, 7.13)	6.37 (4.47, 9.15)
Antiplatelet+Mechanical	2.09 (0.594, 7.3)	2.2 (0.892, 5.55)	3.07 (1.25, 7.79)	3.8 (1.63, 8.89)	4.27 (1.98, 9.51)	6.22 (2.62, 15.4)
DTI	1.77 (0.611, 5.11)	1.87 (0.923, 3.72)	2.59 (1.37, 5.16)	3.2 (1.82, 5.87)	3.62 (1.87, 7.24)	5.27 (3.23, 8.93)
FXIi	1.26 (0.393, 4.18)	1.35 (0.568, 3.12)	1.88 (0.837, 4.17)	2.3 (1.1, 4.86)	2.61 (1.14, 5.98)	3.81 (1.74, 8.12)
LMWH	0.989 (0.396, 2.53)	1.06 (0.652, 1.71)	1.48 (0.984, 2.23)	1.81 (1.41, 2.38)	2.05 (1.33, 3.2)	3 (2.15, 4.15)
FXaI+Mechanical	FXaI+Mechanical	1.06 (0.369, 3.05)	1.49 (0.529, 4.08)	1.83 (0.691, 4.76)	2.08 (0.727, 5.73)	3.03 (1.13, 7.79)
Mechanical	0.942 (0.328, 2.71)	Mechanical	1.4 (0.75, 2.62)	1.71 (1.01, 2.93)	1.95 (1.12, 3.36)	2.83 (1.64, 4.94)
UFH	0.671 (0.245, 1.89)	0.714 (0.382, 1.33)	UFH	1.22 (0.762, 2.02)	1.39 (0.762, 2.54)	2.03 (1.19, 3.42)
VKA	0.547 (0.21, 1.45)	0.584 (0.341, 0.987)	0.817 (0.495, 1.31)	VKA	1.13 (0.715, 1.79)	1.66 (1.07, 2.49)
Antiplatelet	0.48 (0.175, 1.38)	0.513 (0.298, 0.89)	0.719 (0.394, 1.31)	0.888 (0.559, 1.4)	Antiplatelet	1.46 (0.857, 2.47)
Placebo	0.331 (0.128, 0.883)	0.353 (0.202, 0.609)	0.492 (0.292, 0.843)	0.603 (0.401, 0.931)	0.686 (0.404, 1.17)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Table F7.6. Network meta-analysis pairwise results: Total knee replacement, specific intervention comparisons of DVT

	Rivaroxaban	Aspirin+VFP	Fondaparinux	Edoxaban	Apixaban	Darexaban	Flexion
Rivaroxaban	Rivaroxaban	1.31 (0.292, 6.75)	1.86 (0.594, 7.51)	2.2 (0.689, 8.66)	2.41 (0.78, 9.51)	2.52 (0.638, 11.7)	<0.01 (<0.01, >100)
Aspirin+VFP	0.764 (0.148, 3.43)	Aspirin+VFP	1.43 (0.417, 5.32)	1.67 (0.468, 6.21)	1.84 (0.539, 6.73)	1.93 (0.453, 8.28)	<0.01 (<0.01, >100)
Fondaparinux	0.537 (0.133, 1.68)	0.7 (0.188, 2.4)	Fondaparinux	1.17 (0.56, 2.34)	1.3 (0.652, 2.45)	1.35 (0.498, 3.41)	<0.01 (<0.01, >100)
Edoxaban	0.455 (0.116, 1.45)	0.599 (0.161, 2.13)	0.852 (0.428, 1.79)	Edoxaban	1.11 (0.563, 2.23)	1.15 (0.439, 2.98)	<0.01 (<0.01, >100)
Apixaban	0.415 (0.105, 1.28)	0.543 (0.149, 1.86)	0.767 (0.408, 1.53)	0.899 (0.449, 1.78)	Apixaban	1.04 (0.397, 2.61)	<0.01 (<0.01, >100)
Darexaban	0.397 (0.0855, 1.57)	0.518 (0.121, 2.21)	0.743 (0.293, 2.01)	0.87 (0.336, 2.28)	0.965 (0.383, 2.52)	Darexaban	<0.01 (<0.01, >100)
Flexion	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	Flexion
Dabigatran	0.383 (0.096, 1.25)	0.503 (0.133, 1.82)	0.719 (0.356, 1.51)	0.837 (0.398, 1.76)	0.931 (0.459, 1.93)	0.96 (0.363, 2.53)	<0.01 (<0.01, >100)
Enoxaparin+ VFP	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Enoxaparin+ IPC	0.363 (0.0607, 2.03)	0.481 (0.0835, 2.81)	0.692 (0.181, 2.93)	0.805 (0.203, 3.42)	0.895 (0.231, 3.71)	0.922 (0.2, 4.58)	<0.01 (<0.01, >100)
IPC	0.346 (0.0717, 1.33)	0.453 (0.113, 1.63)	0.643 (0.208, 2)	0.756 (0.234, 2.3)	0.835 (0.269, 2.51)	0.863 (0.226, 3.13)	<0.01 (<0.01, >100)
FXIASO	0.276 (0.0645, 1.03)	0.363 (0.0884, 1.42)	0.525 (0.218, 1.27)	0.612 (0.241, 1.5)	0.68 (0.282, 1.59)	0.697 (0.229, 2.1)	<0.01 (<0.01, >100)
Aspirin+IPC	0.275 (0.0395, 1.79)	0.37 (0.0529, 2.48)	0.52 (0.107, 2.67)	0.614 (0.123, 3.09)	0.674 (0.141, 3.4)	0.688 (0.124, 4.03)	<0.01 (<0.01, >100)
Semuloparin	0.267 (0.0668, 0.828)	0.344 (0.0941, 1.2)	0.491 (0.25, 1)	0.575 (0.281, 1.17)	0.639 (0.329, 1.24)	0.661 (0.247, 1.71)	<0.01 (<0.01, >100)
Edoxaban+ VFP	0.216 (0.0404, 0.964)	0.283 (0.0572, 1.37)	0.405 (0.124, 1.32)	0.475 (0.185, 1.18)	0.525 (0.165, 1.67)	0.55 (0.14, 2.06)	<0.01 (<0.01, >100)
Enoxaparin	0.221 (0.0598, 0.62)	0.287 (0.0859, 0.905)	0.409 (0.253, 0.678)	0.478 (0.28, 0.807)	0.53 (0.338, 0.838)	0.548 (0.235, 1.24)	<0.01 (<0.01, >100)
VFP	0.181 (0.0438, 0.605)	0.237 (0.0621, 0.898)	0.339 (0.16, 0.742)	0.397 (0.181, 0.872)	0.44 (0.208, 0.936)	0.459 (0.165, 1.23)	<0.01 (<0.01, >100)
Tinzaparin	0.173 (0.0416, 0.556)	0.223 (0.0615, 0.787)	0.321 (0.147, 0.709)	0.375 (0.162, 0.818)	0.418 (0.191, 0.879)	0.433 (0.148, 1.2)	<0.01 (<0.01, >100)
Heparin	0.149 (0.0378, 0.462)	0.194 (0.0542, 0.676)	0.276 (0.146, 0.555)	0.323 (0.162, 0.644)	0.359 (0.192, 0.685)	0.371 (0.142, 0.946)	<0.01 (<0.01, >100)
Aspirin	0.134 (0.0363, 0.394)	0.175 (0.0599, 0.478)	0.25 (0.121, 0.529)	0.293 (0.135, 0.626)	0.323 (0.159, 0.669)	0.334 (0.12, 0.913)	<0.01 (<0.01, >100)
Warfarin	0.116 (0.0306, 0.334)	0.15 (0.0448, 0.469)	0.215 (0.118, 0.395)	0.25 (0.13, 0.47)	0.28 (0.154, 0.488)	0.288 (0.113, 0.703)	<0.01 (<0.01, >100)
Placebo	0.0726 (0.019, 0.218)	0.0943 (0.0272, 0.314)	0.135 (0.0763, 0.242)	0.157 (0.0883, 0.275)	0.174 (0.0983, 0.31)	0.182 (0.0777, 0.399)	<0.01 (<0.01, >100)
Enoxaparin+ GCS	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, 80.3)

	Dabigatran	Enoxaparin+VFP	Enoxaparin+IPC	IPC	FXIASO	Aspirin+IPC	Semuloparin
Rivaroxaban	2.61 (0.8, 10.4)	<0.01 (<0.01, >100)	2.75 (0.494, 16.5)	2.89 (0.754, 13.9)	3.62 (0.97, 15.5)	3.63 (0.56, 25.3)	3.75 (1.21, 15)
Aspirin+VFP	1.99 (0.549, 7.5)	<0.01 (<0.01, >100)	2.08 (0.356, 12)	2.21 (0.612, 8.87)	2.75 (0.706, 11.3)	2.7 (0.402, 18.9)	2.91 (0.83, 10.6)
Fondaparinux	1.39 (0.661, 2.81)	<0.01 (<0.01, >100)	1.45 (0.342, 5.52)	1.55 (0.501, 4.8)	1.9 (0.788, 4.6)	1.92 (0.375, 9.32)	2.04 (0.997, 4)
Edoxaban	1.19 (0.567, 2.51)	<0.01 (<0.01, >100)	1.24 (0.293, 4.93)	1.32 (0.434, 4.28)	1.63 (0.669, 4.15)	1.63 (0.324, 8.14)	1.74 (0.853, 3.56)
Apixaban	1.07 (0.519, 2.18)	<0.01 (<0.01, >100)	1.12 (0.27, 4.33)	1.2 (0.399, 3.72)	1.47 (0.627, 3.54)	1.48 (0.294, 7.1)	1.57 (0.806, 3.04)
Darexaban	1.04 (0.395, 2.76)	<0.01 (<0.01, >100)	1.08 (0.218, 5.01)	1.16 (0.32, 4.43)	1.43 (0.475, 4.37)	1.45 (0.248, 8.05)	1.51 (0.584, 4.05)
Flexion	>100 (<0.01, >100)	<0.01 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Dabigatran	Dabigatran	<0.01 (<0.01, >100)	1.04 (0.249, 4.15)	1.12 (0.365, 3.62)	1.37 (0.547, 3.46)	1.38 (0.271, 6.79)	1.47 (0.696, 3.1)
Enoxaparin+ VFP	>100 (<0.01, >100)	Enoxaparin+VFP	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Enoxaparin+ IPC	0.962 (0.241, 4.01)	<0.01 (<0.01, >100)	Enoxaparin+IPC	1.07 (0.218, 5.7)	1.31 (0.306, 5.96)	1.32 (0.619, 2.87)	1.4 (0.359, 5.83)
IPC	0.897 (0.277, 2.74)	<0.01 (<0.01, >100)	0.938 (0.175, 4.59)	IPC	1.24 (0.353, 4.28)	1.25 (0.2, 7.45)	1.31 (0.416, 3.97)
FXIASO	0.728 (0.289, 1.83)	<0.01 (<0.01, >100)	0.761 (0.168, 3.27)	0.809 (0.234, 2.83)	FXIASO	1 (0.182, 5.33)	1.07 (0.438, 2.54)
Aspirin+IPC	0.724 (0.147, 3.69)	<0.01 (<0.01, >100)	0.755 (0.348, 1.62)	0.798 (0.134, 5.01)	0.997 (0.188, 5.49)	Aspirin+IPC	1.05 (0.22, 5.37)
Semuloparin	0.682 (0.322, 1.44)	<0.01 (<0.01, >100)	0.714 (0.172, 2.79)	0.765 (0.252, 2.4)	0.937 (0.394, 2.28)	0.95 (0.186, 4.55)	Semuloparin
Edoxaban+ VFP	0.566 (0.168, 1.87)	<0.01 (<0.01, >100)	0.586 (0.106, 3.14)	0.628 (0.146, 2.78)	0.777 (0.208, 2.94)	0.777 (0.12, 4.94)	0.821 (0.255, 2.68)
Enoxaparin	0.569 (0.325, 0.982)	<0.01 (<0.01, >100)	0.592 (0.153, 2.11)	0.636 (0.234, 1.8)	0.778 (0.378, 1.65)	0.784 (0.167, 3.54)	0.832 (0.509, 1.36)
VFP	0.471 (0.212, 1.07)	<0.01 (<0.01, >100)	0.492 (0.115, 1.95)	0.521 (0.162, 1.73)	0.648 (0.254, 1.72)	0.649 (0.124, 3.2)	0.688 (0.316, 1.52)
Tinzaparin	0.448 (0.189, 0.998)	<0.01 (<0.01, >100)	0.463 (0.104, 1.85)	0.503 (0.16, 1.55)	0.614 (0.234, 1.59)	0.615 (0.116, 3.12)	0.654 (0.291, 1.41)
Heparin	0.385 (0.189, 0.777)	<0.01 (<0.01, >100)	0.401 (0.0968, 1.51)	0.429 (0.144, 1.33)	0.525 (0.228, 1.28)	0.533 (0.107, 2.5)	0.562 (0.293, 1.1)
Aspirin	0.348 (0.156, 0.75)	<0.01 (<0.01, >100)	0.363 (0.0861, 1.44)	0.386 (0.168, 0.914)	0.475 (0.191, 1.22)	0.481 (0.095, 2.37)	0.509 (0.238, 1.06)
Warfarin	0.298 (0.152, 0.569)	<0.01 (<0.01, >100)	0.309 (0.0765, 1.15)	0.333 (0.12, 0.921)	0.41 (0.181, 0.937)	0.41 (0.0841, 1.94)	0.437 (0.234, 0.789)
Placebo	0.187 (0.108, 0.323)	<0.01 (<0.01, >100)	0.196 (0.0479, 0.723)	0.21 (0.0723, 0.625)	0.256 (0.112, 0.594)	0.259 (0.0527, 1.21)	0.274 (0.149, 0.503)
Enoxaparin+ GCS	<0.01 (<0.01, <0.01)	<0.01 (<0.01, >100)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)

	Edoxaban+VFP	Enoxaparin	VFP	Tinzaparin	Heparin	Aspirin	Warfarin
Rivaroxaban	4.64 (1.04, 24.8)	4.53 (1.61, 16.7)	5.54 (1.65, 22.8)	5.79 (1.8, 24)	6.73 (2.16, 26.5)	7.48 (2.54, 27.5)	8.65 (2.99, 32.7)
Aspirin+VFP	3.54 (0.728, 17.5)	3.48 (1.1, 11.6)	4.21 (1.11, 16.1)	4.49 (1.27, 16.3)	5.15 (1.48, 18.5)	5.72 (2.09, 16.7)	6.67 (2.13, 22.3)
Fondaparinux	2.47 (0.756, 8.07)	2.45 (1.47, 3.95)	2.95 (1.35, 6.24)	3.11 (1.41, 6.78)	3.62 (1.8, 6.84)	4.01 (1.89, 8.3)	4.66 (2.53, 8.48)
Edoxaban	2.11 (0.845, 5.4)	2.09 (1.24, 3.57)	2.52 (1.15, 5.54)	2.66 (1.22, 6.17)	3.1 (1.55, 6.16)	3.41 (1.6, 7.41)	4 (2.13, 7.7)
Apixaban	1.91 (0.599, 6.08)	1.89 (1.19, 2.96)	2.27 (1.07, 4.8)	2.39 (1.14, 5.25)	2.79 (1.46, 5.22)	3.09 (1.5, 6.3)	3.57 (2.05, 6.49)
Darexaban	1.82 (0.485, 7.14)	1.83 (0.804, 4.26)	2.18 (0.814, 6.06)	2.31 (0.831, 6.78)	2.7 (1.06, 7.05)	2.99 (1.1, 8.35)	3.47 (1.42, 8.86)
Flexion	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Dabigatran	1.77 (0.536, 5.95)	1.76 (1.02, 3.08)	2.12 (0.939, 4.71)	2.23 (1, 5.3)	2.6 (1.29, 5.29)	2.87 (1.33, 6.42)	3.35 (1.76, 6.6)
Enoxaparin+ VFP	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Enoxaparin+ IPC	1.71 (0.318, 9.43)	1.69 (0.475, 6.53)	2.03 (0.513, 8.72)	2.16 (0.54, 9.64)	2.5 (0.662, 10.3)	2.75 (0.696, 11.6)	3.23 (0.868, 13.1)
IPC	1.59 (0.36, 6.86)	1.57 (0.556, 4.28)	1.92 (0.577, 6.17)	1.99 (0.646, 6.27)	2.33 (0.752, 6.97)	2.59 (1.09, 5.95)	3 (1.09, 8.34)
FXIASO	1.29 (0.341, 4.81)	1.29 (0.606, 2.65)	1.54 (0.582, 3.93)	1.63 (0.628, 4.28)	1.91 (0.781, 4.38)	2.1 (0.818, 5.24)	2.44 (1.07, 5.54)
Aspirin+IPC	1.29 (0.202, 8.32)	1.28 (0.283, 5.98)	1.54 (0.312, 8.04)	1.62 (0.321, 8.64)	1.88 (0.4, 9.33)	2.08 (0.422, 10.5)	2.44 (0.517, 11.9)
Semuloparin	1.22 (0.374, 3.92)	1.2 (0.734, 1.97)	1.45 (0.66, 3.17)	1.53 (0.707, 3.44)	1.78 (0.906, 3.41)	1.97 (0.942, 4.2)	2.29 (1.27, 4.27)
Edoxaban+ VFP	Edoxaban+VFP	0.991 (0.337, 2.91)	1.2 (0.353, 3.98)	1.26 (0.37, 4.46)	1.47 (0.459, 4.64)	1.62 (0.484, 5.48)	1.88 (0.604, 5.89)
Enoxaparin	1.01 (0.344, 2.97)	Enoxaparin	1.21 (0.649, 2.2)	1.27 (0.699, 2.41)	1.48 (0.938, 2.29)	1.64 (0.93, 2.87)	1.9 (1.35, 2.77)
VFP	0.833 (0.251, 2.83)	0.829 (0.455, 1.54)	VFP	1.05 (0.454, 2.52)	1.22 (0.58, 2.58)	1.35 (0.6, 3.2)	1.58 (0.795, 3.25)
Tinzaparin	0.795 (0.224, 2.71)	0.788 (0.415, 1.43)	0.948 (0.396, 2.2)	Tinzaparin	1.17 (0.523, 2.45)	1.29 (0.594, 2.71)	1.5 (0.898, 2.48)
Heparin	0.682 (0.216, 2.18)	0.675 (0.437, 1.07)	0.818 (0.387, 1.72)	0.858 (0.408, 1.91)	Heparin	1.11 (0.542, 2.33)	1.29 (0.741, 2.34)
Aspirin	0.616 (0.183, 2.07)	0.611 (0.348, 1.08)	0.739 (0.312, 1.67)	0.776 (0.369, 1.68)	0.904 (0.43, 1.84)	Aspirin	1.16 (0.671, 2.05)
Warfarin	0.531 (0.17, 1.66)	0.526 (0.361, 0.742)	0.633 (0.307, 1.26)	0.667 (0.403, 1.11)	0.778 (0.427, 1.35)	0.86 (0.488, 1.49)	Warfarin
Placebo	0.332 (0.11, 1)	0.329 (0.228, 0.472)	0.398 (0.206, 0.76)	0.418 (0.208, 0.871)	0.489 (0.272, 0.855)	0.54 (0.278, 1.05)	0.628 (0.38, 1.05)
Enoxaparin+ GCS	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)

	Placebo	Enoxaparin+GCS
Rivaroxaban	13.8 (4.58, 52.7)	>100 (>100, >100)
Aspirin+VFP	10.6 (3.18, 36.8)	>100 (>100, >100)
Fondaparinux	7.4 (4.13, 13.1)	>100 (>100, >100)
Edoxaban	6.36 (3.64, 11.3)	>100 (>100, >100)
Apixaban	5.73 (3.23, 10.2)	>100 (>100, >100)
Darexaban	5.51 (2.51, 12.9)	>100 (>100, >100)
Flexion	>100 (<0.01, >100)	>100 (0.0125, >100)
Dabigatran	5.35 (3.1, 9.28)	>100 (>100, >100)
Enoxaparin+ VFP	>100 (<0.01, >100)	>100 (<0.01, >100)
Enoxaparin+ IPC	5.11 (1.38, 20.9)	>100 (>100, >100)
IPC	4.77 (1.6, 13.8)	>100 (>100, >100)
FXIASO	3.9 (1.68, 8.91)	>100 (>100, >100)
Aspirin+IPC	3.86 (0.828, 19)	>100 (>100, >100)
Semuloparin	3.65 (1.99, 6.72)	>100 (>100, >100)
Edoxaban+ VFP	3.01 (1, 9.06)	>100 (>100, >100)
Enoxaparin	3.04 (2.12, 4.38)	>100 (>100, >100)
VFP	2.51 (1.32, 4.85)	>100 (>100, >100)
Tinzaparin	2.39 (1.15, 4.81)	>100 (>100, >100)
Heparin	2.05 (1.17, 3.68)	>100 (>100, >100)
Aspirin	1.85 (0.951, 3.59)	>100 (>100, >100)
Warfarin	1.59 (0.954, 2.63)	>100 (>100, >100)
Placebo	Placebo	>100 (67.6, >100)
Enoxaparin+ GCS	<0.01 (<0.01, 0.0148)	Enoxaparin+GCS

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DVT = deep vein thrombosis, FXIASO = factor XI antisense oligonuclide, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, TKR = total hip replacement, VFP = venous foot pump.

Table F7.7. Network meta-analysis pairwise results: Total knee replacement, intervention class comparisons of major bleeding

	VKA	LMWH	UFH	Placebo	DTI	FXaI+ Mechanical	FXaI	FXIi
VKA	VKA	2.1 (0.533, 8.63)	2.14 (0.108, 43.4)	2.25 (0.191, 24.2)	2.71 (0.48, 18.3)	4.01 (0.171, 116)	3.72 (0.696, 25.6)	>100 (<0.01, >100)
LMWH	0.477 (0.116, 1.88)	LMWH	1.02 (0.0713, 14.6)	1.07 (0.135, 7.29)	1.28 (0.433, 4.52)	1.94 (0.106, 39.5)	1.78 (0.612, 6.27)	>100 (<0.01, >100)
UFH	0.467 (0.023, 9.25)	0.979 (0.0686, 14)	UFH	1.04 (0.0362, 28.3)	1.26 (0.0745, 25.1)	1.87 (0.0363, 110)	1.75 (0.106, 35.6)	>100 (<0.01, >100)
Placebo	0.445 (0.0413, 5.22)	0.938 (0.137, 7.4)	0.965 (0.0354, 27.6)	Placebo	1.21 (0.171, 10.8)	1.8 (0.062, 68)	1.67 (0.206, 18.3)	>100 (<0.01, >100)
DTI	0.369 (0.0546, 2.09)	0.78 (0.221, 2.31)	0.791 (0.0398, 13.4)	0.828 (0.0922, 5.84)	DTI	1.5 (0.0626, 35)	1.38 (0.282, 7.17)	>100 (<0.01, >100)
FXaI+ Mechanical	0.25 (0.00862, 5.86)	0.517 (0.0253, 9.46)	0.533 (0.00912, 27.6)	0.555 (0.0147, 16.1)	0.668 (0.0286, 16)	FXaI+ Mechanical	0.93 (0.062, 14.6)	>100 (<0.01, >100)
FXaI	0.269 (0.0391, 1.44)	0.563 (0.16, 1.64)	0.572 (0.0281, 9.46)	0.598 (0.0545, 4.86)	0.723 (0.139, 3.54)	1.08 (0.0687, 16.1)	FXaI	>100 (<0.01, >100)
FXIi	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	FXIi

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, TKR = total knee replacement, UFH = unfractionated heparin, VKA = vitamin K antagonist.

Table F7.8. Network meta-analysis pairwise results: Total knee replacement, specific intervention comparisons of major bleeding

	Warfarin	FXIASO	Eribaxaban	Apixaban	TAK442	Semuloparin	Enoxaparin	Heparin
Warfarin	Warfarin	<0.01 (<0.01, >100)	0.8 (0.0141, 25)	1.05 (0.0756, 16.2)	1.03 (0.0398, 24.9)	1.2 (0.0635, 23.7)	1.69 (0.359, 8.82)	1.73 (0.0844, 37.4)
FXIASO	>100 (<0.01, >100)	FXIASO	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Eribaxaban	1.25 (0.04, 70.7)	<0.01 (<0.01, >100)	Eribaxaban	1.32 (0.0335, 95.4)	1.29 (0.0204, 125)	1.49 (0.0289, 137)	2.08 (0.106, 89.2)	2.19 (0.0398, 199)
Apixaban	0.949 (0.0616, 13.2)	<0.01 (<0.01, >100)	0.76 (0.0105, 29.8)	Apixaban	0.958 (0.0277, 29.6)	1.14 (0.0411, 30.6)	1.6 (0.187, 14.2)	1.63 (0.0549, 46.1)
TAK442	0.972 (0.0402, 25.1)	<0.01 (<0.01, >100)	0.778 (0.00797, 48.9)	1.04 (0.0338, 36.1)	TAK442	1.17 (0.0278, 55.9)	1.65 (0.11, 28.4)	1.71 (0.0388, 77.4)
Semuloparin	0.834 (0.0422, 15.7)	<0.01 (<0.01, >100)	0.672 (0.0073, 34.5)	0.878 (0.0327, 24.3)	0.856 (0.0179, 36)	Semuloparin	1.41 (0.116, 18)	1.45 (0.0398, 54.6)
Enoxaparin	0.591 (0.113, 2.79)	<0.01 (<0.01, >100)	0.481 (0.0112, 9.41)	0.624 (0.0704, 5.36)	0.605 (0.0352, 9.1)	0.707 (0.0554, 8.59)	Enoxaparin	1.03 (0.0724, 13.8)
Heparin	0.579 (0.0267, 11.8)	<0.01 (<0.01, >100)	0.456 (0.00502, 25.1)	0.613 (0.0217, 18.2)	0.586 (0.0129, 25.7)	0.689 (0.0183, 25.1)	0.97 (0.0725, 13.8)	Heparin
Dabigatran	0.465 (0.0552, 2.74)	<0.01 (<0.01, >100)	0.371 (0.00687, 7.96)	0.499 (0.0362, 4.78)	0.47 (0.0202, 7.99)	0.554 (0.0301, 7.73)	0.787 (0.221, 2.13)	0.806 (0.0408, 12.4)
Placebo	0.415 (0.0287, 5.31)	<0.01 (<0.01, >100)	0.328 (0.00466, 12.2)	0.434 (0.0218, 8.46)	0.426 (0.0116, 12.5)	0.498 (0.018, 12)	0.703 (0.0859, 5.34)	0.706 (0.0249, 20)
Tinzaparin	0.296 (0.0245, 3.13)	<0.01 (<0.01, >100)	0.227 (0.00199, 15.6)	0.31 (0.00882, 11)	0.298 (0.0048, 16.2)	0.351 (0.00719, 16.1)	0.498 (0.0267, 9.2)	0.501 (0.00998, 24.8)
Edoxaban+ VFP	0.0958 (<0.01, 6.2)	<0.01 (<0.01, >100)	0.0738 (<0.01, 10.7)	0.102 (<0.01, 8.96)	0.0952 (<0.01, 11.7)	0.116 (<0.01, 11.8)	0.166 (<0.01, 8.09)	0.164 (<0.01, 18.6)
Edoxaban	0.109 (<0.01, 2.67)	<0.01 (<0.01, >100)	0.0836 (<0.01, 5.56)	0.114 (<0.01, 3.88)	0.107 (<0.01, 5.5)	0.129 (<0.01, 5.66)	0.187 (<0.01, 3.12)	0.184 (<0.01, 8.8)
Fondaparinux	0.037 (<0.01, 0.847)	<0.01 (<0.01, >100)	0.0284 (<0.01, 1.7)	0.0386 (<0.01, 1.21)	0.0364 (<0.01, 1.79)	0.043 (<0.01, 1.8)	0.0641 (<0.01, 0.917)	0.0623 (<0.01, 2.7)
Darexaban	<0.01 (<0.01, 0.272)	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.297)	<0.01 (<0.01, 0.293)	<0.01 (<0.01, 0.335)	<0.01 (<0.01, 0.399)	<0.01 (<0.01, 0.396)	<0.01 (<0.01, 0.577)

	Dabigatran	Placebo	Tinzaparin	Edoxaban+VFP	Edoxaban	Fondaparinux	Darexaban
Warfarin	2.15 (0.365, 18.1)	2.41 (0.188, 34.9)	3.38 (0.32, 40.8)	10.4 (0.161, >100)	9.2 (0.374, >100)	27.1 (1.18, >100)	>100 (3.68, >100)
FXIASO	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Eribaxaban	2.7 (0.126, 146)	3.05 (0.0819, 215)	4.41 (0.064, 501)	13.6 (0.0933, >100)	12 (0.18, >100)	35.2 (0.588, >100)	>100 (3.37, >100)
Apixaban	2 (0.209, 27.6)	2.3 (0.118, 45.9)	3.23 (0.0913, 113)	9.83 (0.112, >100)	8.73 (0.258, >100)	25.9 (0.828, >100)	>100 (3.41, >100)
TAK442	2.13 (0.125, 49.6)	2.35 (0.0798, 86.6)	3.35 (0.0617, 208)	10.5 (0.0854, >100)	9.33 (0.182, >100)	27.5 (0.559, >100)	>100 (2.98, >100)
Semuloparin	1.8 (0.129, 33.2)	2.01 (0.0832, 55.6)	2.85 (0.062, 139)	8.61 (0.0849, >100)	7.78 (0.177, >100)	23.2 (0.556, >100)	>100 (2.51, >100)
Enoxaparin	1.27 (0.469, 4.53)	1.42 (0.187, 11.6)	2.01 (0.109, 37.5)	6.04 (0.124, >100)	5.35 (0.321, >100)	15.6 (1.09, >100)	>100 (2.53, >100)
Heparin	1.24 (0.0808, 24.5)	1.42 (0.05, 40.2)	2 (0.0403, 100)	6.11 (0.0537, >100)	5.45 (0.114, >100)	16.1 (0.371, >100)	>100 (1.73, >100)
Dabigatran	Dabigatran	1.12 (0.13, 8.34)	1.59 (0.0605, 31.7)	4.73 (0.0736, >100)	4.21 (0.185, >100)	12.2 (0.613, >100)	>100 (1.85, >100)
Placebo	0.895 (0.12, 7.7)	Placebo	1.41 (0.0385, 50.1)	4.26 (0.0525, >100)	3.9 (0.119, >100)	11.2 (0.365, >100)	>100 (1.89, >100)
Tinzaparin	0.63 (0.0315, 16.5)	0.708 (0.02, 26)	Tinzaparin	2.98 (0.0231, >100)	2.68 (0.0475, >100)	7.96 (0.154, >100)	>100 (0.844, >100)
Edoxaban+ VFP	0.212 (<0.01, 13.6)	0.235 (<0.01, 19)	0.335 (<0.01, 43.2)	Edoxaban+VFP	0.922 (0.0693, 12.6)	2.76 (0.0139, >100)	>100 (0.163, >100)
Edoxaban	0.238 (<0.01, 5.42)	0.257 (<0.01, 8.39)	0.374 (<0.01, 21)	1.08 (0.0792, 14.4)	Edoxaban	2.96 (0.0299, >100)	>100 (0.232, >100)
Fondaparinux	0.0822 (<0.01, 1.63)	0.0891 (<0.01, 2.74)	0.126 (<0.01, 6.49)	0.362 (<0.01, 72.2)	0.338 (<0.01, 33.5)	Fondaparinux	>100 (0.0891, >100)
Darexaban	<0.01 (<0.01, 0.54)	<0.01 (<0.01, 0.53)	<0.01 (<0.01, 1.18)	<0.01 (<0.01, 6.15)	<0.01 (<0.01, 4.32)	<0.01 (<0.01, 11.2)	Darexaban

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: FXIASO = factor XI antisense oligonuclide, TKR = total knee replacement.

Table F7.9. Network meta-analysis pairwise results: Hip fracture surgery, intervention class comparisons of DVT

	UFH	FXaI	LMWH	Placebo
UFH	UFH	1.38 (0.167, 15.5)	3.25 (0.45, 24)	8.84 (0.908, 103)
FXaI	0.725 (0.0646, 5.99)	FXaI	2.4 (0.654, 6.18)	**6.41 (1.31, 26.4)**
LMWH	0.308 (0.0417, 2.22)	0.417 (0.162, 1.53)	LMWH	2.73 (0.779, 10.9)
Placebo	0.113 (0.0097, 1.1)	**0.156 (0.0379, 0.762)**	0.367 (0.0917, 1.28)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, UFH = unfractionated heparin.

Table F7.10. Network meta-analysis pairwise results: Hip fracture surgery, specific intervention comparisons of DVT

	Heparin	Fondaparinux	Dalteparin	Semuloparin	Enoxaparin	Edoxaban	Placebo
Heparin	Heparin	2.53 (0.214, 28.5)	3.26 (0.562, 20.1)	5.41 (0.366, 84.4)	7.43 (0.786, 76.9)	18.1 (0.572, 1.15e+03)	13.4 (1.38, 135)
Fondaparinux	0.395 (0.035, 4.67)	Fondaparinux	1.31 (0.248, 7.11)	2.12 (0.35, 14.8)	**2.94 (1.03, 9.49)**	7.04 (0.415, 280)	5.32 (1.27, 25)
Dalteparin	0.307 (0.0499, 1.78)	0.766 (0.141, 4.02)	Dalteparin	1.64 (0.214, 13.1)	2.26 (0.564, 9.75)	5.42 (0.265, 239)	4.08 (0.977, 17.5)
Semuloparin	0.185 (0.0119, 2.73)	0.472 (0.0675, 2.86)	0.609 (0.0763, 4.67)	Semuloparin	1.38 (0.307, 6.15)	3.26 (0.156, 138)	2.5 (0.332, 18.5)
Enoxaparin	0.135 (0.013, 1.27)	**0.34 (0.105, 0.97)**	0.442 (0.103, 1.77)	0.726 (0.162, 3.25)	Enoxaparin	2.32 (0.163, 78)	1.81 (0.462, 7.06)
Edoxaban	0.0551 (0.000873, 1.75)	0.142 (0.00358, 2.41)	0.185 (0.00419, 3.78)	0.307 (0.00722, 6.43)	0.43 (0.0128, 6.13)	Edoxaban	0.755 (0.0179, 15.1)
Placebo	**0.0744 (0.00741, 0.725)**	**0.188 (0.0401, 0.788)**	0.245 (0.0572, 1.02)	0.401 (0.054, 3.02)	0.554 (0.142, 2.16)	1.32 (0.0664, 55.9)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class. Statistically significant differences are bold.
Abbreviations: DVT = deep vein thrombosis.

Table F7.11. Network meta-analysis pairwise results: Hip fracture surgery, intervention class comparisons of major bleeding

	Antiplatelet	VKA	Placebo	LMWH	FXaI
Antiplatelet	Antiplatelet	7.54 (0.406, >100)	7.83 (0.423, >100)	>100 (3.73, >100)	>100 (5.34, >100)
VKA	0.133 (<0.01, 2.46)	VKA	1.04 (0.086, 13.1)	>100 (0.659, >100)	>100 (0.934, >100)
Placebo	0.128 (<0.01, 2.37)	0.964 (0.077, 11.6)	Placebo	>100 (0.862, >100)	>100 (1.23, >100)
LMWH	<0.01 (<0.01, 0.268)	<0.01 (<0.01, 1.52)	<0.01 (<0.01, 1.16)	LMWH	1.25 (0.289, 8.69)
FXaI	<0.01 (<0.01, 0.187)	<0.01 (<0.019, 1.07)	<0.01 (<0.01, 0.816)	0.803 (0.115, 3.46)	FXaI

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: FXaI = factor Xa inhibitor, HFx = hip fracture, LMWH = low molecular weight heparin, VKA = vitamin K antagonist.

Table F7.12. Network meta-analysis pairwise results: Hip fracture surgery, specific intervention comparisons of major bleeding

	Aspirin	Warfarin	Placebo	Dalteparin	Edoxaban	Enoxaparin	Semuloparin	Fondaparinux
Aspirin	Aspirin	7.76 (0.359, >100)	8.11 (0.377, >100)	>100 (1.35, >100)	>100 (1.64, >100)	>100 (6.35, >100)	>100 (8.44, >100)	>100 (12.3, >100)
Warfarin	0.129 (<0.01, 2.79)	Warfarin	1.03 (0.076, 13.9)	>100 (0.191, >100)	>100 (0.207, >100)	>100 (0.976, >100)	>100 (1.23, >100)	>100 (1.8, >100)
Placebo	0.123 (<0.01, 2.65)	0.971 (0.072, 13.2)	Placebo	>100 (0.242, >100)	>100 (0.258, >100)	>100 (1.24, >100)	>100 (1.62, >100)	>100 (2.45, >100)
Dalteparin	<0.01 (<0.01, 0.741)	<0.01 (<0.01, 5.25)	<0.01 (<0.01, 4.13)	Dalteparin	1.27 (0.00549, 384)	2.47 (0.0801, 134)	4.52 (0.0609, 577)	4.27 (0.097, 483)
Edoxaban	<0.01 (<0.01, 0.61)	<0.01 (<0.01, 4.83)	<0.01 (<0.01, 3.87)	0.785 (0.00261, 182)	Edoxaban	2.03 (0.0303, 145)	3.61 (0.0246, 568)	3.4 (0.0388, 508)
Enoxaparin	<0.01 (<0.01, 0.157)	<0.01 (<0.01, 1.02)	<0.01 (<0.01, 0.805)	0.405 (0.00747, 12.5)	0.493 (0.0069, 33)	Enoxaparin	1.79 (0.125, 28.4)	1.56 (0.29, 20.6)
Semuloparin	<0.01 (<0.01, 0.118)	<0.01 (<0.01, 0.81)	<0.01 (<0.01, 0.618)	0.221 (0.00173, 16.4)	0.277 (0.00176, 40.6)	0.559 (0.0352, 7.97)	Semuloparin	0.903 (0.0402, 40)
Fondaparinux	<0.01 (<0.01, 0.0812)	<0.01 (<0.01, 0.556)	<0.01 (<0.01, 0.408)	0.234 (0.00207, 10.3)	0.294 (0.00197, 25.8)	0.64 (0.0486, 3.45)	1.11 (0.025, 24.9)	Fondaparinux

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: HFx = hip fracture.

Appendix G. Pairwise Results of Network Meta-Analyses With Informative Priors

Table G1. Network meta-analysis pairwise results: Total hip replacement, intervention class comparisons of total DVT

	LMWH+ Mechanical	FXaI	DTI	FEI	Mechanical	Antiplatelet	LMWH	VKA	UFH	Placebo
LMWH+ Mechanical	LMWH+Mechanical	2.96 (1, 9.7)	3.35 (1.1, 11.2)	3.29 (0.618, 19.1)	4.07 (1.28, 13.9)	4.08 (1.05, 16.2)	4.94 (1.79, 15.3)	7.41 (2.41, 24.7)	7.61 (2.62, 25)	11.4 (3.97, 36.4)
FXaI	0.338 (0.103, 0.997)	FXaI	1.14 (0.621, 2.02)	1.11 (0.305, 4.03)	1.38 (0.719, 2.51)	1.37 (0.524, 3.33)	1.68 (1.15, 2.39)	2.51 (1.37, 4.42)	2.58 (1.55, 4.22)	3.85 (2.43, 6.05)
DTI	0.298 (0.0889, 0.91)	0.881 (0.496, 1.61)	DTI	0.975 (0.243, 4.1)	1.21 (0.607, 2.37)	1.21 (0.444, 3.12)	1.48 (0.925, 2.35)	2.21 (1.15, 4.24)	2.27 (1.39, 3.79)	3.38 (1.95, 6.05)
FEI	0.304 (0.0524, 1.62)	0.904 (0.248, 3.27)	1.03 (0.244, 4.12)	FEI	1.24 (0.296, 5.07)	1.24 (0.251, 5.85)	1.52 (0.391, 5.75)	2.26 (0.539, 9.19)	2.32 (0.581, 9.11)	3.48 (0.885, 13.5)
Mechanical	0.246 (0.072, 0.78)	0.727 (0.398, 1.39)	0.825 (0.423, 1.65)	0.805 (0.197, 3.37)	Mechanical	1 (0.383, 2.52)	1.22 (0.739, 2.06)	1.82 (1.07, 3.15)	1.87 (1.06, 3.45)	2.79 (1.59, 5.1)
Antiplatelet	0.245 (0.0616, 0.95)	0.728 (0.301, 1.91)	0.827 (0.32, 2.25)	0.808 (0.171, 3.98)	0.999 (0.397, 2.61)	Antiplatelet	1.22 (0.535, 2.97)	1.82 (0.8, 4.34)	1.88 (0.778, 4.89)	2.8 (1.24, 6.76)
LMWH	0.203 (0.0655, 0.559)	0.596 (0.419, 0.869)	0.677 (0.426, 1.08)	0.66 (0.174, 2.56)	0.821 (0.486, 1.35)	0.82 (0.337, 1.87)	LMWH	1.49 (0.932, 2.37)	1.54 (1.09, 2.2)	2.3 (1.66, 3.22)
VKA	0.135 (0.0405, 0.415)	0.398 (0.226, 0.732)	0.453 (0.236, 0.871)	0.443 (0.109, 1.85)	0.55 (0.317, 0.934)	0.549 (0.23, 1.25)	0.67 (0.421, 1.07)	VKA	1.03 (0.585, 1.84)	1.54 (0.901, 2.69)
UFH	0.131 (0.04, 0.381)	0.387 (0.237, 0.644)	0.44 (0.264, 0.721)	0.431 (0.11, 1.72)	0.534 (0.29, 0.942)	0.532 (0.204, 1.28)	0.651 (0.454, 0.92)	0.972 (0.544, 1.71)	UFH	1.49 (0.936, 2.4)
Placebo	0.0878 (0.0275, 0.252)	0.26 (0.165, 0.412)	0.295 (0.165, 0.514)	0.287 (0.0743, 1.13)	0.358 (0.196, 0.628)	0.357 (0.148, 0.807)	0.435 (0.31, 0.603)	0.651 (0.372, 1.11)	0.67 (0.417, 1.07)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FEI=factor XIII inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist

Table G2. Network meta-analysis pairwise results: Total hip replacement, specific intervention comparisons of total DVT

	Enoxaparin+IPC	Apixaban	Edoxaban	Enoxaparin+GCS	Semuloparin	Desirudin	Fondaparinux
Enoxaparin+IPC	Enoxaparin+IPC	5.75 (0.509, 197)	7.05 (0.588, 256)	7.64 (0.882, 238)	10.1 (0.91, 336)	10.4 (1.02, 342)	11.7 (1.15, 378)
Apixaban	0.174 (0.00506, 1.96)	Apixaban	1.23 (0.331, 4.53)	1.36 (0.32, 5.48)	1.76 (0.57, 5.36)	1.84 (0.694, 4.83)	2.02 (0.801, 5.68)
Edoxaban	0.142 (0.0039, 1.7)	0.816 (0.221, 3.02)	Edoxaban	1.11 (0.235, 5.06)	1.43 (0.407, 5.05)	1.49 (0.494, 4.66)	1.65 (0.554, 5.34)
Enoxaparin+GCS	0.131 (0.00421, 1.13)	0.735 (0.183, 3.12)	0.904 (0.198, 4.26)	Enoxaparin+GCS	1.29 (0.33, 5.19)	1.35 (0.398, 4.88)	1.5 (0.455, 5.53)
Semuloparin	0.0994 (0.00298, 1.1)	0.57 (0.186, 1.75)	0.701 (0.198, 2.46)	0.773 (0.193, 3.03)	Semuloparin	1.05 (0.421, 2.6)	1.15 (0.489, 3.08)
Desirudin	0.0957 (0.00293, 0.985)	0.543 (0.207, 1.44)	0.67 (0.215, 2.03)	0.74 (0.205, 2.51)	0.951 (0.385, 2.38)	Desirudin	1.09 (0.562, 2.42)
Fondaparinux	0.0856 (0.00265, 0.869)	0.496 (0.176, 1.25)	0.605 (0.187, 1.81)	0.669 (0.181, 2.2)	0.87 (0.325, 2.04)	0.914 (0.414, 1.78)	Fondaparinux
Darexaban	0.0801 (0.0024, 0.855)	0.457 (0.149, 1.37)	0.563 (0.157, 1.92)	0.621 (0.157, 2.32)	0.803 (0.278, 2.24)	0.842 (0.341, 2.02)	0.927 (0.392, 2.34)
VFP	0.0759 (0.0023, 0.802)	0.43 (0.152, 1.24)	0.528 (0.159, 1.75)	0.585 (0.155, 2.1)	0.754 (0.282, 2.07)	0.791 (0.366, 1.74)	0.875 (0.403, 2.11)
Dabigatran	0.0623 (0.00186, 0.642)	0.352 (0.13, 0.973)	0.434 (0.134, 1.38)	0.48 (0.131, 1.69)	0.62 (0.237, 1.59)	0.652 (0.298, 1.38)	0.716 (0.346, 1.64)
Aspirin	0.0583 (0.00178, 0.634)	0.335 (0.106, 1.06)	0.411 (0.113, 1.48)	0.455 (0.111, 1.77)	0.586 (0.198, 1.75)	0.614 (0.244, 1.57)	0.678 (0.275, 1.84)
Dalteparin	0.0585 (0.00182, 0.603)	0.336 (0.118, 0.867)	0.411 (0.126, 1.25)	0.454 (0.122, 1.53)	0.592 (0.217, 1.43)	0.619 (0.29, 1.19)	0.681 (0.324, 1.43)
Enoxaparin	0.0539 (0.00169, 0.513)	0.306 (0.132, 0.696)	0.377 (0.134, 1.01)	0.417 (0.128, 1.27)	0.537 (0.25, 1.13)	0.565 (0.336, 0.925)	0.619 (0.386, 1.1)
IPC	0.0509 (0.00156, 0.546)	0.291 (0.0993, 0.853)	0.358 (0.105, 1.19)	0.396 (0.102, 1.46)	0.51 (0.185, 1.4)	0.535 (0.232, 1.22)	0.591 (0.261, 1.45)
Rivaroxaban	0.0414 (0.00124, 0.442)	0.237 (0.0783, 0.719)	0.292 (0.0835, 0.997)	0.322 (0.0831, 1.2)	0.417 (0.144, 1.19)	0.438 (0.18, 1.05)	0.483 (0.204, 1.21)
TB402	0.0364 (0.000924, 0.532)	0.213 (0.0424, 1.07)	0.261 (0.0469, 1.44)	0.287 (0.048, 1.69)	0.374 (0.0764, 1.82)	0.393 (0.0894, 1.68)	0.434 (0.101, 1.95)
Tinzaparin	0.0372 (0.00118, 0.373)	0.215 (0.0772, 0.54)	0.263 (0.0828, 0.781)	0.291 (0.0804, 0.951)	0.377 (0.144, 0.892)	0.396 (0.188, 0.761)	0.434 (0.216, 0.885)
Heparin	0.038 (0.00118, 0.373)	0.218 (0.0861, 0.517)	0.268 (0.0893, 0.745)	0.295 (0.0855, 0.927)	0.384 (0.162, 0.843)	0.402 (0.237, 0.629)	0.441 (0.244, 0.826)
Warfarin	0.0315 (0.000977, 0.322)	0.182 (0.0647, 0.475)	0.222 (0.0688, 0.68)	0.245 (0.0665, 0.825)	0.318 (0.119, 0.777)	0.333 (0.157, 0.658)	0.367 (0.176, 0.783)
Placebo	0.0226 (0.000707, 0.217)	0.13 (0.0514, 0.308)	0.159 (0.0533, 0.445)	0.176 (0.0521, 0.533)	0.228 (0.0971, 0.502)	0.239 (0.128, 0.414)	0.263 (0.147, 0.483)

	Darexaban	VFP	Dabigatran	Aspirin	Dalteparin	Enoxaparin	IPC
Enoxaparin+IPC	12.5 (1.17, 416)	13.2 (1.25, 435)	16.1 (1.56, 537)	17.1 (1.58, 563)	17.1 (1.66, 550)	18.5 (1.95, 593)	19.6 (1.83, 640)
Apixaban	2.19 (0.731, 6.73)	2.32 (0.805, 6.56)	2.84 (1.03, 7.72)	2.99 (0.942, 9.39)	2.97 (1.15, 8.5)	3.26 (1.44, 7.56)	3.44 (1.17, 10.1)
Edoxaban	1.78 (0.521, 6.38)	1.89 (0.571, 6.29)	2.3 (0.726, 7.47)	2.43 (0.677, 8.83)	2.44 (0.802, 7.92)	2.65 (0.995, 7.49)	2.79 (0.838, 9.52)
Enoxaparin+GCS	1.61 (0.432, 6.36)	1.71 (0.476, 6.46)	2.08 (0.591, 7.64)	2.2 (0.564, 9)	2.2 (0.655, 8.21)	2.4 (0.79, 7.82)	2.53 (0.685, 9.76)
Semuloparin	1.24 (0.446, 3.6)	1.33 (0.484, 3.55)	1.61 (0.628, 4.22)	1.71 (0.57, 5.06)	1.69 (0.702, 4.61)	1.86 (0.882, 4.01)	1.96 (0.716, 5.39)
Desirudin	1.19 (0.494, 2.94)	1.26 (0.574, 2.74)	1.53 (0.723, 3.35)	1.63 (0.638, 4.1)	1.62 (0.843, 3.44)	1.77 (1.08, 2.97)	1.87 (0.817, 4.31)
Fondaparinux	1.08 (0.427, 2.55)	1.14 (0.475, 2.48)	1.4 (0.609, 2.89)	1.47 (0.545, 3.64)	1.47 (0.697, 3.09)	1.62 (0.913, 2.59)	1.69 (0.688, 3.83)
Darexaban	Darexaban	1.06 (0.393, 2.73)	1.29 (0.506, 3.24)	1.37 (0.462, 3.92)	1.36 (0.568, 3.47)	1.49 (0.711, 3.1)	1.57 (0.579, 4.22)
VFP	0.942 (0.366, 2.55)	VFP	1.21 (0.525, 2.92)	1.29 (0.479, 3.5)	1.29 (0.598, 3.02)	1.41 (0.756, 2.69)	1.49 (0.599, 3.74)
Dabigatran	0.774 (0.309, 1.98)	0.825 (0.342, 1.91)	Dabigatran	1.06 (0.394, 2.83)	1.05 (0.49, 2.45)	1.16 (0.65, 2.05)	1.22 (0.496, 2.95)
Aspirin	0.73 (0.255, 2.17)	0.774 (0.286, 2.09)	0.939 (0.353, 2.54)	Aspirin	0.996 (0.444, 2.43)	1.09 (0.498, 2.46)	1.15 (0.459, 2.91)
Dalteparin	0.733 (0.288, 1.76)	0.777 (0.332, 1.67)	0.95 (0.408, 2.04)	1 (0.412, 2.25)	Dalteparin	1.1 (0.605, 1.85)	1.15 (0.542, 2.27)
Enoxaparin	0.67 (0.322, 1.41)	0.711 (0.372, 1.32)	0.865 (0.487, 1.54)	0.919 (0.406, 2.01)	0.913 (0.541, 1.65)	Enoxaparin	1.05 (0.526, 2.08)
IPC	0.637 (0.237, 1.73)	0.673 (0.268, 1.67)	0.823 (0.34, 2.02)	0.871 (0.344, 2.18)	0.868 (0.441, 1.85)	0.951 (0.481, 1.9)	IPC
Rivaroxaban	0.523 (0.19, 1.44)	0.555 (0.209, 1.41)	0.671 (0.267, 1.7)	0.713 (0.248, 2.04)	0.712 (0.298, 1.8)	0.779 (0.375, 1.61)	0.819 (0.306, 2.17)
TB402	0.464 (0.0995, 2.23)	0.495 (0.109, 2.21)	0.604 (0.133, 2.64)	0.639 (0.13, 3.05)	0.64 (0.148, 2.89)	0.696 (0.174, 2.77)	0.734 (0.157, 3.37)
Tinzaparin	0.468 (0.193, 1.09)	0.497 (0.218, 1.05)	0.606 (0.27, 1.26)	0.643 (0.264, 1.44)	0.638 (0.343, 1.21)	0.701 (0.408, 1.12)	0.736 (0.34, 1.49)
Heparin	0.476 (0.21, 1.05)	0.505 (0.251, 0.953)	0.616 (0.308, 1.17)	0.651 (0.275, 1.46)	0.649 (0.382, 1.14)	0.711 (0.497, 0.972)	0.749 (0.355, 1.52)
Warfarin	0.395 (0.159, 0.961)	0.42 (0.179, 0.916)	0.512 (0.224, 1.11)	0.54 (0.244, 1.14)	0.538 (0.336, 0.895)	0.592 (0.332, 1.01)	0.621 (0.345, 1.07)
Placebo	0.284 (0.131, 0.598)	0.3 (0.148, 0.575)	0.366 (0.185, 0.688)	0.388 (0.173, 0.814)	0.386 (0.223, 0.694)	0.423 (0.299, 0.577)	0.445 (0.214, 0.886)

	Rivaroxaban	TB402	Tinzaparin	Heparin	Warfarin	Placebo
Enoxaparin+IPC	24.1 (2.26, 808)	27.5 (1.88, >100)	26.9 (2.68, 851)	26.3 (2.68, 845)	31.7 (3.1, >100)	44.2 (4.61, >100)
Apixaban	4.21 (1.39, 12.8)	4.7 (0.938, 23.6)	4.66 (1.85, 12.9)	4.59 (1.93, 11.6)	5.51 (2.11, 15.5)	7.71 (3.25, 19.5)
Edoxaban	3.42 (1, 12)	3.83 (0.695, 21.3)	3.8 (1.28, 12.1)	3.73 (1.34, 11.2)	4.5 (1.47, 14.5)	6.28 (2.25, 18.7)
Enoxaparin+GCS	3.11 (0.834, 12)	3.48 (0.592, 20.9)	3.44 (1.05, 12.4)	3.39 (1.08, 11.7)	4.08 (1.21, 15)	5.67 (1.88, 19.2)
Semuloparin	2.4 (0.839, 6.96)	2.67 (0.55, 13.1)	2.65 (1.12, 6.92)	2.61 (1.19, 6.19)	3.15 (1.29, 8.4)	4.38 (1.99, 10.3)
Desirudin	2.28 (0.956, 5.55)	2.54 (0.594, 11.2)	2.52 (1.31, 5.31)	2.49 (1.59, 4.22)	3 (1.52, 6.38)	4.18 (2.42, 7.79)
Fondaparinux	2.07 (0.823, 4.9)	2.3 (0.513, 9.9)	2.31 (1.13, 4.62)	2.27 (1.21, 4.1)	2.72 (1.28, 5.67)	3.8 (2.07, 6.78)
Darexaban	1.91 (0.693, 5.28)	2.15 (0.449, 10.1)	2.13 (0.919, 5.17)	2.1 (0.952, 4.75)	2.53 (1.04, 6.31)	3.53 (1.67, 7.65)
VFP	1.8 (0.708, 4.8)	2.02 (0.452, 9.19)	2.01 (0.954, 4.6)	1.98 (1.05, 3.98)	2.38 (1.09, 5.59)	3.33 (1.74, 6.76)
Dabigatran	1.49 (0.588, 3.75)	1.66 (0.379, 7.54)	1.65 (0.795, 3.71)	1.62 (0.857, 3.25)	1.95 (0.901, 4.47)	2.73 (1.45, 5.39)
Aspirin	1.4 (0.491, 4.02)	1.57 (0.328, 7.7)	1.56 (0.695, 3.79)	1.54 (0.683, 3.64)	1.85 (0.88, 4.1)	2.58 (1.23, 5.77)
Dalteparin	1.4 (0.554, 3.35)	1.56 (0.346, 6.76)	1.57 (0.825, 2.91)	1.54 (0.875, 2.62)	1.86 (1.12, 2.98)	2.59 (1.44, 4.48)
Enoxaparin	1.28 (0.622, 2.67)	1.44 (0.361, 5.75)	1.43 (0.893, 2.45)	1.41 (1.03, 2.01)	1.69 (0.994, 3.01)	2.36 (1.73, 3.34)
IPC	1.22 (0.462, 3.27)	1.36 (0.297, 6.36)	1.36 (0.671, 2.94)	1.34 (0.66, 2.82)	1.61 (0.936, 2.9)	2.25 (1.13, 4.68)
Rivaroxaban	Rivaroxaban	1.11 (0.346, 3.63)	1.11 (0.481, 2.7)	1.1 (0.502, 2.46)	1.32 (0.548, 3.28)	1.84 (0.876, 3.95)
TB402	0.898 (0.276, 2.89)	TB402	1 (0.238, 4.43)	0.981 (0.24, 4.09)	1.18 (0.273, 5.21)	1.65 (0.414, 6.67)
Tinzaparin	0.898 (0.37, 2.08)	1 (0.226, 4.21)	Tinzaparin	0.986 (0.551, 1.72)	1.18 (0.666, 2.07)	1.65 (1, 2.68)
Heparin	0.913 (0.406, 1.99)	1.02 (0.245, 4.17)	1.01 (0.581, 1.82)	Heparin	1.2 (0.678, 2.17)	1.68 (1.09, 2.58)
Warfarin	0.757 (0.305, 1.83)	0.845 (0.192, 3.67)	0.845 (0.483, 1.5)	0.832 (0.462, 1.48)	Warfarin	1.4 (0.793, 2.42)
Placebo	0.543 (0.253, 1.14)	0.605 (0.15, 2.42)	0.605 (0.374, 1)	0.596 (0.387, 0.92)	0.717 (0.414, 1.26)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, VFP = venous foot pump.

Table G3. Network meta-analysis pairwise results: Total hip replacement, intervention class comparisons of major bleeding

	Mechanical	VKA	Placebo	LMWH	DTI	FXaI	Antiplatelet	UFH	FEI
Mechanical	Mechanical	>100 (12.1, >100)	>100 (18.2, >100)	>100 (25.6, >100)	>100 (32.7, >100)	>100 (33.2, >100)	>100 (<0.01, >100)	>100 (52, >100)	>100 (>100, >100)
VKA	<0.01 (<0.01, 0.0828)	VKA	1.54 (0.494, 4.95)	1.97 (1.15, 3.49)	2.53 (1.3, 5.05)	2.64 (1.41, 5.07)	>100 (<0.01, >100)	4.32 (1.99, 9.59)	>100 (>100, >100)
Placebo	<0.01 (<0.01, 0.0548)	0.651 (0.202, 2.02)	Placebo	1.28 (0.46, 3.58)	1.65 (0.546, 4.87)	1.72 (0.603, 4.87)	>100 (<0.01, >100)	2.82 (0.884, 8.59)	>100 (>100, >100)
LMWH	<0.01 (<0.01, 0.039)	0.508 (0.287, 0.872)	0.781 (0.279, 2.17)	LMWH	1.28 (0.868, 1.91)	1.34 (0.967, 1.87)	>100 (<0.01, >100)	2.18 (1.29, 3.86)	>100 (>100, >100)
DTI	<0.01 (<0.01, 0.0306)	0.396 (0.198, 0.768)	0.608 (0.206, 1.83)	0.779 (0.523, 1.15)	DTI	1.04 (0.623, 1.74)	>100 (<0.01, >100)	1.71 (0.871, 3.39)	>100 (>100, >100)
FXaI	<0.01 (<0.01, 0.0301)	0.378 (0.197, 0.711)	0.581 (0.205, 1.66)	0.745 (0.535, 1.03)	0.957 (0.574, 1.6)	FXaI	>100 (<0.01, >100)	1.63 (0.874, 3.11)	>100 (>100, >100)
Antiplatelet	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	Antiplatelet	<0.01 (<0.01, >100)	>100 (<0.01, >100)
UFH	<0.01 (<0.01, 0.0192)	0.232 (0.104, 0.503)	0.355 (0.116, 1.13)	0.459 (0.259, 0.778)	0.586 (0.295, 1.15)	0.614 (0.322, 1.14)	>100 (<0.01, >100)	UFH	>100 (72.4, >100)
FEI	<0.01 (<0.01, <0.01)	<0.01 (<0.01, 0.00329)	<0.01 (<0.01, 0.00513)	<0.01 (<0.01, 0.00628)	<0.01 (<0.01, 0.00791)	<0.01 (<0.01, 0.0084)	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.0138)	FEI

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Abbreviations: DTI = direct thrombin inhibitor, FEI=factor XIII inhibitor, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist

Table G4. Network meta-analysis pairwise results: Total hip replacement, specific intervention comparisons of major bleeding

	IPC	Semuloparin	Warfarin	Dalteparin	Edoxaban	Tinzaparin	Placebo
IPC	IPC	>100 (4.95, >100)	>100 (7, >100)	>100 (9.62, >100)	>100 (11.9, >100)	>100 (11.7, >100)	>100 (14, >100)
Semuloparin	<0.01 (<0.01, 0.202)	Semuloparin	1.38 (0.342, 6.58)	2.13 (0.384, 13.9)	2.27 (0.372, 14.6)	2.38 (0.493, 13.6)	2.86 (0.602, 15.2)
Warfarin	<0.01 (<0.01, 0.143)	0.724 (0.152, 2.93)	Warfarin	1.53 (0.546, 4.57)	1.65 (0.328, 7.68)	1.72 (0.673, 4.42)	2.05 (0.514, 8.17)
Dalteparin	<0.01 (<0.01, 0.104)	0.469 (0.0717, 2.61)	0.653 (0.219, 1.83)	Dalteparin	1.07 (0.173, 6.34)	1.13 (0.269, 4.38)	1.35 (0.236, 7.13)
Edoxaban	<0.01 (<0.01, 0.0843)	0.44 (0.0686, 2.68)	0.607 (0.13, 3.04)	0.937 (0.158, 5.78)	Edoxaban	1.06 (0.193, 6.09)	1.25 (0.223, 7.8)
Tinzaparin	<0.01 (<0.01, 0.0851)	0.419 (0.0737, 2.03)	0.58 (0.226, 1.49)	0.889 (0.228, 3.71)	0.943 (0.164, 5.18)	Tinzaparin	1.18 (0.254, 5.63)
Placebo	<0.01 (<0.01, 0.0715)	0.35 (0.0659, 1.66)	0.487 (0.122, 1.95)	0.742 (0.14, 4.23)	0.8 (0.128, 4.48)	0.849 (0.178, 3.94)	Placebo
Darexaban	<0.01 (<0.01, 0.0877)	0.267 (0.00888, 16.9)	0.376 (0.0146, 21.5)	0.596 (0.0185, 32)	0.629 (0.0191, 38.3)	0.672 (0.0227, 42.4)	0.773 (0.0281, 49.2)
Enoxaparin	<0.01 (<0.01, 0.0509)	0.268 (0.0686, 0.812)	0.371 (0.155, 0.799)	0.565 (0.158, 2.04)	0.599 (0.141, 2.33)	0.632 (0.211, 1.82)	0.757 (0.25, 2.21)
Desirudin	<0.01 (<0.01, 0.0522)	0.268 (0.0575, 1.02)	0.37 (0.12, 1.07)	0.567 (0.13, 2.49)	0.603 (0.119, 2.86)	0.635 (0.175, 2.3)	0.754 (0.206, 2.74)
Aspirin	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
Rivaroxaban	<0.01 (<0.01, 0.0484)	0.237 (0.0466, 1.05)	0.331 (0.0897, 1.14)	0.506 (0.101, 2.58)	0.539 (0.0989, 2.75)	0.572 (0.129, 2.4)	0.683 (0.183, 2.33)
Apixaban	<0.01 (<0.01, 0.0428)	0.219 (0.0472, 0.822)	0.305 (0.0993, 0.859)	0.464 (0.106, 1.99)	0.493 (0.0996, 2.27)	0.52 (0.14, 1.83)	0.621 (0.169, 2.22)
Dabigatran	<0.01 (<0.01, 0.0345)	0.183 (0.0435, 0.62)	0.254 (0.0928, 0.641)	0.387 (0.0967, 1.52)	0.414 (0.09, 1.74)	0.434 (0.13, 1.39)	0.52 (0.153, 1.67)
Fondaparinux	<0.01 (<0.01, 0.0323)	0.167 (0.0392, 0.558)	0.232 (0.0862, 0.575)	0.354 (0.0896, 1.41)	0.377 (0.0823, 1.6)	0.398 (0.121, 1.26)	0.476 (0.141, 1.5)
Heparin	<0.01 (<0.01, 0.0225)	0.121 (0.0279, 0.428)	0.168 (0.0595, 0.436)	0.257 (0.0621, 1.04)	0.27 (0.0588, 1.17)	0.289 (0.0823, 0.955)	0.345 (0.101, 1.12)
TB402	<0.01 (<0.01, <0.01)	<0.01 (<0.01, 0.0208)	<0.01 (<0.01, 0.0256)	<0.01 (<0.01, 0.0428)	<0.01 (<0.01, 0.0534)	<0.01 (<0.01, 0.0437)	<0.01 (<0.01, 0.0544)

	Darexaban	Enoxaparin	Desirudin	Aspirin	Rivaroxaban	Apixaban	Dabigatran
IPC	>100 (11.4, >100)	>100 (19.7, >100)	>100 (19.1, >100)	>100 (<0.01, >100)	>100 (20.7, >100)	>100 (23.3, >100)	>100 (29, >100)
Semuloparin	3.75 (0.0593, 113)	3.73 (1.23, 14.6)	3.73 (0.98, 17.4)	>100 (<0.01, >100)	4.21 (0.953, 21.5)	4.57 (1.22, 21.2)	5.47 (1.61, 23)
Warfarin	2.66 (0.0466, 68.6)	2.7 (1.25, 6.45)	2.7 (0.931, 8.35)	>100 (<0.01, >100)	3.02 (0.877, 11.2)	3.28 (1.16, 10.1)	3.93 (1.56, 10.8)
Dalteparin	1.68 (0.0313, 54)	1.77 (0.491, 6.34)	1.76 (0.402, 7.7)	>100 (<0.01, >100)	1.98 (0.388, 9.92)	2.16 (0.503, 9.44)	2.58 (0.657, 10.3)
Edoxaban	1.59 (0.0261, 52.5)	1.67 (0.429, 7.09)	1.66 (0.35, 8.4)	>100 (<0.01, >100)	1.86 (0.364, 10.1)	2.03 (0.44, 10)	2.41 (0.574, 11.1)
Tinzaparin	1.49 (0.0236, 44)	1.58 (0.549, 4.75)	1.57 (0.435, 5.72)	>100 (<0.01, >100)	1.75 (0.416, 7.75)	1.92 (0.547, 7.13)	2.3 (0.719, 7.72)
Placebo	1.29 (0.0203, 35.6)	1.32 (0.453, 4)	1.33 (0.365, 4.86)	>100 (<0.01, >100)	1.46 (0.429, 5.47)	1.61 (0.449, 5.93)	1.92 (0.597, 6.54)
Darexaban	Darexaban	1.02 (0.0451, 55)	1.02 (0.0419, 58.4)	>100 (<0.01, >100)	1.15 (0.0448, 68.8)	1.24 (0.0514, 72.8)	1.49 (0.0642, 80.4)
Enoxaparin	0.979 (0.0182, 22.2)	Enoxaparin	0.994 (0.482, 2.03)	>100 (<0.01, >100)	1.11 (0.429, 2.9)	1.22 (0.6, 2.51)	1.46 (0.888, 2.4)
Desirudin	0.981 (0.0171, 23.9)	1.01 (0.493, 2.07)	Desirudin	>100 (<0.01, >100)	1.12 (0.344, 3.69)	1.23 (0.451, 3.42)	1.46 (0.612, 3.55)
Aspirin	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	Aspirin	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
Rivaroxaban	0.871 (0.0145, 22.3)	0.901 (0.345, 2.33)	0.894 (0.271, 2.91)	>100 (<0.01, >100)	Rivaroxaban	1.1 (0.332, 3.62)	1.31 (0.443, 3.89)
Apixaban	0.804 (0.0137, 19.4)	0.822 (0.398, 1.67)	0.813 (0.292, 2.22)	>100 (<0.01, >100)	0.909 (0.276, 3.02)	Apixaban	1.2 (0.499, 2.84)
Dabigatran	0.673 (0.0124, 15.6)	0.687 (0.417, 1.13)	0.685 (0.282, 1.64)	>100 (<0.01, >100)	0.764 (0.257, 2.26)	0.834 (0.352, 2)	Dabigatran
Fondaparinux	0.612 (0.0113, 14.6)	0.629 (0.392, 0.982)	0.625 (0.262, 1.45)	>100 (<0.01, >100)	0.697 (0.242, 1.98)	0.762 (0.326, 1.79)	0.913 (0.466, 1.79)
Heparin	0.44 (0.00889, 10.6)	0.456 (0.257, 0.798)	0.451 (0.18, 1.11)	89.2 (<0.01, >100)	0.505 (0.17, 1.5)	0.551 (0.225, 1.39)	0.663 (0.31, 1.41)
TB402	<0.01 (<0.01, 0.103)	<0.01 (<0.01, 0.072)	<0.01 (<0.01, 0.0704)	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.0803)	<0.01 (<0.01, 0.0894)	<0.01 (<0.01, 0.107)

	Fondaparinux	Heparin	TB402
IPC	>100 (30.9, >100)	>100 (44.5, >100)	>100 (>100, >100)
Semuloparin	5.97 (1.79, 25.5)	8.28 (2.34, 35.8)	>100 (48, >100)
Warfarin	4.3 (1.74, 11.6)	5.95 (2.3, 16.8)	>100 (39, >100)
Dalteparin	2.82 (0.71, 11.2)	3.89 (0.965, 16.1)	>100 (23.4, >100)
Edoxaban	2.65 (0.627, 12.2)	3.7 (0.853, 17)	>100 (18.7, >100)
Tinzaparin	2.51 (0.797, 8.28)	3.46 (1.05, 12.1)	>100 (22.9, >100)
Placebo	2.1 (0.665, 7.09)	2.9 (0.891, 9.91)	>100 (18.4, >100)
Darexaban	1.64 (0.0684, 88.4)	2.27 (0.094, 112)	>100 (9.66, >100)
Enoxaparin	1.59 (1.02, 2.55)	2.19 (1.25, 3.89)	>100 (13.9, >100)
Desirudin	1.6 (0.692, 3.82)	2.22 (0.898, 5.54)	>100 (14.2, >100)
Aspirin	<0.01 (<0.01, >100)	0.0112 (<0.01, >100)	>100 (<0.01, >100)
Rivaroxaban	1.43 (0.506, 4.12)	1.98 (0.667, 5.89)	>100 (12.5, >100)
Apixaban	1.31 (0.559, 3.07)	1.81 (0.718, 4.45)	>100 (11.2, >100)
Dabigatran	1.1 (0.559, 2.15)	1.51 (0.708, 3.23)	>100 (9.33, >100)
Fondaparinux	Fondaparinux	1.38 (0.666, 2.88)	>100 (8.57, >100)
Heparin	0.724 (0.347, 1.5)	Heparin	>100 (6.15, >100)
TB402	<0.01 (<0.01, 0.117)	<0.01 (<0.01, 0.162)	TB402

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: IPC = intermittent pneumatic compression.

Table G5. Network meta-analysis pairwise results: Total knee replacement, intervention class comparisons of total DVT

	LMWH+Mechanical	FXaI	Antiplatelet+ Mechanical	DTI	FXIi	LMWH
LMWH+Mechanical	LMWH+Mechanical	1.12 (0.498, 2.59)	1.16 (0.601, 2.21)	1.34 (0.528, 3.53)	1.86 (0.66, 5.51)	2.37 (1.08, 5.41)
FXaI	0.895 (0.386, 2.01)	FXaI	1.04 (0.446, 2.31)	1.2 (0.692, 2.06)	1.66 (0.823, 3.41)	2.12 (1.71, 2.66)
Antiplatelet+Mechanical	0.864 (0.453, 1.67)	0.963 (0.432, 2.24)	Antiplatelet+Mechanical	1.15 (0.455, 3.02)	1.61 (0.567, 4.66)	2.04 (0.937, 4.65)
DTI	0.746 (0.284, 1.89)	0.835 (0.485, 1.45)	0.866 (0.331, 2.2)	DTI	1.39 (0.596, 3.26)	1.77 (1.06, 2.98)
FXIi	0.539 (0.182, 1.52)	0.602 (0.294, 1.22)	0.622 (0.215, 1.77)	0.72 (0.307, 1.68)	FXIi	1.27 (0.65, 2.5)
LMWH	0.421 (0.185, 0.927)	0.472 (0.376, 0.584)	0.49 (0.215, 1.07)	0.566 (0.336, 0.941)	0.784 (0.399, 1.54)	LMWH
FXaI+Mechanical	0.42 (0.118, 1.4)	0.469 (0.187, 1.14)	0.486 (0.139, 1.62)	0.561 (0.195, 1.6)	0.78 (0.245, 2.47)	0.996 (0.387, 2.49)
Mechanical	0.4 (0.157, 0.976)	0.447 (0.267, 0.744)	0.463 (0.188, 1.11)	0.535 (0.268, 1.06)	0.743 (0.325, 1.69)	0.948 (0.586, 1.53)
UFH	0.284 (0.114, 0.688)	0.318 (0.203, 0.498)	0.329 (0.133, 0.796)	0.38 (0.198, 0.73)	0.528 (0.244, 1.15)	0.673 (0.454, 1)
VKA	0.234 (0.1, 0.524)	0.262 (0.185, 0.359)	0.271 (0.117, 0.6)	0.313 (0.175, 0.55)	0.435 (0.211, 0.895)	0.554 (0.429, 0.707)
Antiplatelet	0.206 (0.0874, 0.465)	0.231 (0.143, 0.365)	0.239 (0.106, 0.51)	0.275 (0.142, 0.535)	0.383 (0.171, 0.856)	0.488 (0.318, 0.747)
Placebo	0.141 (0.0586, 0.329)	0.158 (0.11, 0.222)	0.163 (0.0684, 0.376)	0.189 (0.112, 0.313)	0.261 (0.124, 0.56)	0.334 (0.241, 0.462)

	FXaI+Mechanical	Mechanical	UFH	VKA	Antiplatelet	Placebo
LMWH+Mechanical	2.38 (0.713, 8.45)	2.5 (1.03, 6.37)	3.52 (1.45, 8.74)	4.28 (1.91, 9.96)	4.85 (2.15, 11.4)	7.12 (3.04, 17.1)
FXaI	2.13 (0.88, 5.36)	2.24 (1.34, 3.74)	3.14 (2.01, 4.93)	3.82 (2.79, 5.4)	4.34 (2.74, 6.97)	6.34 (4.5, 9.06)
Antiplatelet+Mechanical	2.06 (0.616, 7.17)	2.16 (0.902, 5.32)	3.04 (1.26, 7.53)	3.69 (1.67, 8.57)	4.18 (1.96, 9.42)	6.13 (2.66, 14.6)
DTI	1.78 (0.624, 5.13)	1.87 (0.943, 3.74)	2.63 (1.37, 5.04)	3.19 (1.82, 5.71)	3.63 (1.87, 7.04)	5.29 (3.19, 8.9)
FXIi	1.28 (0.404, 4.08)	1.35 (0.59, 3.08)	1.9 (0.873, 4.11)	2.3 (1.12, 4.73)	2.61 (1.17, 5.84)	3.83 (1.79, 8.06)
LMWH	1 (0.401, 2.58)	1.05 (0.654, 1.71)	1.49 (0.995, 2.2)	1.8 (1.42, 2.33)	2.05 (1.34, 3.15)	3 (2.16, 4.15)
FXaI+Mechanical	FXaI+Mechanical	1.05 (0.367, 2.92)	1.48 (0.531, 4.03)	1.8 (0.677, 4.68)	2.04 (0.728, 5.58)	2.97 (1.12, 7.76)
Mechanical	0.951 (0.342, 2.72)	Mechanical	1.41 (0.754, 2.59)	1.71 (1.01, 2.89)	1.95 (1.14, 3.32)	2.84 (1.67, 4.85)
UFH	0.675 (0.248, 1.88)	0.711 (0.386, 1.33)	UFH	1.22 (0.77, 1.96)	1.38 (0.772, 2.47)	2.02 (1.2, 3.38)
VKA	0.557 (0.214, 1.48)	0.584 (0.346, 0.988)	0.823 (0.51, 1.3)	VKA	1.14 (0.728, 1.75)	1.66 (1.1, 2.49)
Antiplatelet	0.49 (0.179, 1.37)	0.514 (0.301, 0.88)	0.725 (0.405, 1.29)	0.879 (0.571, 1.37)	Antiplatelet	1.46 (0.871, 2.46)
Placebo	0.336 (0.129, 0.892)	0.353 (0.206, 0.6)	0.495 (0.296, 0.834)	0.603 (0.402, 0.909)	0.684 (0.406, 1.15)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Abbreviations: DTI = direct thrombin inhibitor, DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist

Table G6. Network meta-analysis pairwise results: Total knee replacement, specific intervention comparisons of total DVT

	Rivaroxaban	Aspirin+VFP	Fondaparinux	Edoxaban	Apixaban	Darexaban	Dabigatran
Rivaroxaban	Rivaroxaban	1.33 (0.313, 6.64)	1.9 (0.648, 7.07)	2.24 (0.732, 8.59)	2.5 (0.866, 9.16)	2.63 (0.708, 11.2)	2.69 (0.858, 10.3)
Aspirin+VFP	0.751 (0.15, 3.19)	Aspirin+VFP	1.44 (0.435, 4.94)	1.69 (0.501, 5.95)	1.89 (0.592, 6.34)	1.96 (0.486, 8)	2.01 (0.599, 7.1)
Fondaparinux	0.527 (0.142, 1.54)	0.695 (0.202, 2.3)	Fondaparinux	1.18 (0.6, 2.25)	1.31 (0.736, 2.28)	1.36 (0.535, 3.28)	1.4 (0.721, 2.69)
Edoxaban	0.446 (0.116, 1.37)	0.591 (0.168, 2)	0.85 (0.444, 1.67)	Edoxaban	1.11 (0.607, 2.07)	1.16 (0.448, 2.85)	1.19 (0.597, 2.36)
Apixaban	0.4 (0.109, 1.15)	0.53 (0.158, 1.69)	0.762 (0.438, 1.36)	0.899 (0.484, 1.65)	Apixaban	1.05 (0.415, 2.44)	1.07 (0.573, 1.99)
Darexaban	0.381 (0.0893, 1.41)	0.511 (0.125, 2.06)	0.733 (0.305, 1.87)	0.861 (0.351, 2.23)	0.957 (0.41, 2.41)	Darexaban	1.03 (0.417, 2.68)
Dabigatran	0.372 (0.0974, 1.17)	0.497 (0.141, 1.67)	0.713 (0.371, 1.39)	0.839 (0.423, 1.67)	0.935 (0.503, 1.74)	0.975 (0.374, 2.4)	Dabigatran
Enoxaparin+IPC	0.36 (0.0609, 1.9)	0.482 (0.0903, 2.61)	0.696 (0.195, 2.72)	0.819 (0.22, 3.24)	0.912 (0.258, 3.49)	0.944 (0.219, 4.29)	0.977 (0.263, 3.9)
IPC	0.34 (0.0749, 1.24)	0.45 (0.125, 1.6)	0.648 (0.225, 1.89)	0.763 (0.255, 2.28)	0.852 (0.303, 2.35)	0.876 (0.251, 3.04)	0.908 (0.306, 2.69)
FXIASO	0.274 (0.0666, 0.935)	0.366 (0.0947, 1.32)	0.522 (0.231, 1.18)	0.618 (0.259, 1.43)	0.686 (0.316, 1.48)	0.715 (0.242, 2.02)	0.735 (0.31, 1.72)
Aspirin+IPC	0.271 (0.0401, 1.69)	0.362 (0.0579, 2.26)	0.523 (0.118, 2.4)	0.616 (0.139, 2.87)	0.688 (0.159, 3.1)	0.712 (0.138, 3.71)	0.728 (0.161, 3.46)
Semuloparin	0.256 (0.0697, 0.754)	0.339 (0.0999, 1.11)	0.488 (0.269, 0.899)	0.575 (0.3, 1.08)	0.64 (0.371, 1.09)	0.67 (0.265, 1.59)	0.685 (0.356, 1.31)
Enoxaparin+VFP	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
Edoxaban+VFP	0.207 (0.0419, 0.895)	0.277 (0.0596, 1.25)	0.4 (0.132, 1.22)	0.471 (0.19, 1.15)	0.524 (0.176, 1.55)	0.549 (0.146, 1.92)	0.56 (0.179, 1.75)
Enoxaparin	0.213 (0.0605, 0.575)	0.282 (0.0881, 0.854)	0.405 (0.263, 0.632)	0.478 (0.288, 0.784)	0.531 (0.373, 0.753)	0.555 (0.238, 1.2)	0.568 (0.339, 0.946)
VFP	0.175 (0.0453, 0.555)	0.232 (0.0642, 0.808)	0.334 (0.169, 0.674)	0.394 (0.191, 0.82)	0.439 (0.228, 0.843)	0.458 (0.171, 1.17)	0.469 (0.225, 0.976)
Flexion	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
Tinzaparin	0.165 (0.0438, 0.517)	0.22 (0.064, 0.728)	0.316 (0.159, 0.637)	0.374 (0.177, 0.77)	0.415 (0.216, 0.786)	0.431 (0.16, 1.12)	0.445 (0.211, 0.927)
Heparin	0.143 (0.0384, 0.424)	0.189 (0.0559, 0.616)	0.271 (0.151, 0.503)	0.32 (0.167, 0.611)	0.357 (0.21, 0.616)	0.374 (0.144, 0.89)	0.381 (0.199, 0.731)
Aspirin	0.132 (0.0364, 0.368)	0.174 (0.0632, 0.463)	0.251 (0.127, 0.497)	0.295 (0.143, 0.603)	0.329 (0.172, 0.616)	0.341 (0.128, 0.874)	0.352 (0.167, 0.723)
Warfarin	0.111 (0.0311, 0.312)	0.148 (0.0464, 0.444)	0.212 (0.124, 0.365)	0.25 (0.137, 0.448)	0.278 (0.172, 0.443)	0.29 (0.117, 0.67)	0.298 (0.161, 0.541)
Placebo	0.0696 (0.019, 0.2)	0.0925 (0.0274, 0.295)	0.133 (0.0783, 0.226)	0.156 (0.0913, 0.265)	0.174 (0.105, 0.284)	0.182 (0.079, 0.388)	0.186 (0.111, 0.311)
Enoxaparin+GCS	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)

	Enoxaparin+IPC	IPC	FXIASO	Aspirin+IPC	Semuloparin	Enoxaparin+VFP	Edoxaban+VFP
Rivaroxaban	2.78 (0.525, 16.4)	2.94 (0.807, 13.4)	3.65 (1.07, 15)	3.69 (0.592, 25)	3.91 (1.33, 14.3)	>100 (<0.01, >100)	4.84 (1.12, 23.8)
Aspirin+VFP	2.07 (0.383, 11.1)	2.22 (0.626, 8.01)	2.74 (0.76, 10.6)	2.76 (0.443, 17.3)	2.95 (0.901, 10)	>100 (<0.01, >100)	3.61 (0.803, 16.8)
Fondaparinux	1.44 (0.368, 5.14)	1.54 (0.529, 4.44)	1.91 (0.846, 4.32)	1.91 (0.417, 8.44)	2.05 (1.11, 3.72)	>100 (<0.01, >100)	2.5 (0.821, 7.55)
Edoxaban	1.22 (0.309, 4.55)	1.31 (0.438, 3.92)	1.62 (0.701, 3.87)	1.62 (0.348, 7.22)	1.74 (0.926, 3.33)	>100 (<0.01, >100)	2.13 (0.869, 5.26)
Apixaban	1.1 (0.286, 3.87)	1.17 (0.425, 3.3)	1.46 (0.677, 3.16)	1.45 (0.323, 6.3)	1.56 (0.916, 2.7)	>100 (<0.01, >100)	1.91 (0.645, 5.68)
Darexaban	1.06 (0.233, 4.57)	1.14 (0.329, 3.98)	1.4 (0.494, 4.14)	1.4 (0.269, 7.23)	1.49 (0.63, 3.78)	>100 (<0.01, >100)	1.82 (0.52, 6.85)
Dabigatran	1.02 (0.256, 3.81)	1.1 (0.371, 3.27)	1.36 (0.581, 3.22)	1.37 (0.289, 6.21)	1.46 (0.761, 2.81)	>100 (<0.01, >100)	1.78 (0.573, 5.57)
Enoxaparin+IPC	Enoxaparin+IPC	1.08 (0.223, 5.3)	1.34 (0.324, 5.58)	1.34 (0.652, 2.75)	1.42 (0.398, 5.51)	>100 (<0.01, >100)	1.74 (0.356, 9.06)
IPC	0.925 (0.189, 4.49)	IPC	1.24 (0.381, 4.02)	1.24 (0.216, 6.91)	1.33 (0.465, 3.79)	>100 (<0.01, >100)	1.63 (0.392, 6.67)
FXIASO	0.748 (0.179, 3.09)	0.806 (0.249, 2.62)	FXIASO	0.995 (0.2, 4.93)	1.07 (0.482, 2.39)	>100 (<0.01, >100)	1.31 (0.376, 4.45)
Aspirin+IPC	0.748 (0.363, 1.53)	0.805 (0.145, 4.63)	1.01 (0.203, 5)	Aspirin+IPC	1.07 (0.243, 4.92)	>100 (<0.01, >100)	1.31 (0.227, 7.83)
Semuloparin	0.703 (0.181, 2.51)	0.751 (0.264, 2.15)	0.932 (0.418, 2.08)	0.934 (0.203, 4.12)	Semuloparin	>100 (<0.01, >100)	1.22 (0.408, 3.69)
Enoxaparin+VFP	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	Enoxaparin+VFP	<0.01 (<0.01, >100)
Edoxaban+VFP	0.576 (0.11, 2.81)	0.614 (0.15, 2.55)	0.765 (0.224, 2.66)	0.765 (0.128, 4.41)	0.822 (0.271, 2.45)	>100 (<0.01, >100)	Edoxaban+VFP
Enoxaparin	0.581 (0.16, 1.95)	0.626 (0.237, 1.65)	0.772 (0.39, 1.54)	0.774 (0.178, 3.21)	0.829 (0.552, 1.24)	>100 (<0.01, >100)	1.01 (0.363, 2.84)
VFP	0.479 (0.12, 1.83)	0.516 (0.171, 1.58)	0.638 (0.266, 1.56)	0.637 (0.135, 2.95)	0.685 (0.346, 1.36)	>100 (<0.01, >100)	0.836 (0.264, 2.68)
Flexion	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	81.4 (<0.01, >100)	<0.01 (<0.01, >100)
Tinzaparin	0.458 (0.112, 1.71)	0.488 (0.171, 1.41)	0.605 (0.251, 1.44)	0.606 (0.126, 2.79)	0.648 (0.331, 1.28)	>100 (<0.01, >100)	0.792 (0.249, 2.52)
Heparin	0.391 (0.102, 1.4)	0.419 (0.148, 1.2)	0.52 (0.232, 1.15)	0.523 (0.115, 2.3)	0.558 (0.317, 0.99)	>100 (<0.01, >100)	0.681 (0.226, 2.08)
Aspirin	0.361 (0.0896, 1.35)	0.387 (0.172, 0.855)	0.479 (0.202, 1.15)	0.48 (0.101, 2.18)	0.514 (0.263, 0.997)	>100 (<0.01, >100)	0.629 (0.198, 1.95)
Warfarin	0.306 (0.08, 1.07)	0.328 (0.126, 0.861)	0.406 (0.188, 0.866)	0.407 (0.0902, 1.73)	0.435 (0.259, 0.725)	97.4 (<0.01, >100)	0.53 (0.18, 1.55)
Placebo	0.191 (0.0499, 0.666)	0.205 (0.0743, 0.57)	0.253 (0.117, 0.551)	0.253 (0.0556, 1.08)	0.272 (0.159, 0.463)	59.6 (<0.01, >100)	0.332 (0.116, 0.944)
Enoxaparin+GCS	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, <0.01)	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.0114)

	Enoxaparin	VFP	Flexion	Tinzaparin	Heparin	Aspirin	Warfarin
Rivaroxaban	4.69 (1.74, 16.5)	5.73 (1.8, 22.1)	>100 (<0.01, >100)	6.05 (1.94, 22.8)	7 (2.36, 26)	7.57 (2.72, 27.4)	8.99 (3.21, 32.2)
Aspirin+VFP	3.55 (1.17, 11.3)	4.32 (1.24, 15.6)	>100 (<0.01, >100)	4.54 (1.37, 15.6)	5.28 (1.62, 17.9)	5.75 (2.16, 15.8)	6.77 (2.25, 21.6)
Fondaparinux	2.47 (1.58, 3.8)	3 (1.48, 5.93)	>100 (<0.01, >100)	3.16 (1.57, 6.29)	3.68 (1.99, 6.62)	3.99 (2.01, 7.86)	4.71 (2.74, 8.07)
Edoxaban	2.09 (1.28, 3.48)	2.54 (1.22, 5.24)	>100 (<0.01, >100)	2.68 (1.3, 5.65)	3.13 (1.64, 5.99)	3.39 (1.66, 7.02)	4 (2.23, 7.32)
Apixaban	1.88 (1.33, 2.68)	2.28 (1.19, 4.39)	>100 (<0.01, >100)	2.41 (1.27, 4.62)	2.8 (1.62, 4.77)	3.04 (1.62, 5.8)	3.59 (2.26, 5.82)
Darexaban	1.8 (0.83, 4.2)	2.18 (0.857, 5.86)	>100 (<0.01, >100)	2.32 (0.897, 6.27)	2.68 (1.12, 6.94)	2.93 (1.14, 7.79)	3.44 (1.49, 8.55)
Dabigatran	1.76 (1.06, 2.95)	2.13 (1.02, 4.43)	>100 (<0.01, >100)	2.25 (1.08, 4.74)	2.62 (1.37, 5.02)	2.84 (1.38, 5.98)	3.36 (1.85, 6.22)
Enoxaparin+IPC	1.72 (0.512, 6.23)	2.09 (0.546, 8.35)	>100 (<0.01, >100)	2.18 (0.586, 8.9)	2.56 (0.713, 9.79)	2.77 (0.739, 11.2)	3.27 (0.934, 12.5)
IPC	1.6 (0.605, 4.22)	1.94 (0.633, 5.86)	>100 (<0.01, >100)	2.05 (0.71, 5.85)	2.39 (0.834, 6.74)	2.58 (1.17, 5.8)	3.05 (1.16, 7.96)
FXIASO	1.3 (0.65, 2.57)	1.57 (0.641, 3.75)	>100 (<0.01, >100)	1.65 (0.695, 3.98)	1.92 (0.866, 4.3)	2.09 (0.873, 4.96)	2.47 (1.15, 5.31)
Aspirin+IPC	1.29 (0.312, 5.63)	1.57 (0.339, 7.41)	>100 (<0.01, >100)	1.65 (0.358, 7.91)	1.91 (0.436, 8.72)	2.08 (0.459, 9.94)	2.46 (0.578, 11.1)
Semuloparin	1.21 (0.803, 1.81)	1.46 (0.734, 2.89)	>100 (<0.01, >100)	1.54 (0.784, 3.02)	1.79 (1.01, 3.16)	1.95 (1, 3.8)	2.3 (1.38, 3.87)
Enoxaparin+VFP	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	0.0123 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	0.0103 (<0.01, >100)
Edoxaban+VFP	0.99 (0.352, 2.75)	1.2 (0.374, 3.79)	>100 (<0.01, >100)	1.26 (0.396, 4.02)	1.47 (0.481, 4.43)	1.59 (0.512, 5.05)	1.89 (0.645, 5.54)
Enoxaparin	Enoxaparin	1.21 (0.694, 2.1)	>100 (<0.01, >100)	1.28 (0.75, 2.2)	1.49 (0.989, 2.22)	1.61 (0.958, 2.75)	1.9 (1.39, 2.64)
VFP	0.825 (0.476, 1.44)	VFP	>100 (<0.01, >100)	1.06 (0.485, 2.32)	1.23 (0.614, 2.42)	1.33 (0.626, 2.87)	1.58 (0.834, 3.01)
Flexion	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	Flexion	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)	<0.01 (<0.01, >100)
Tinzaparin	0.783 (0.455, 1.33)	0.948 (0.431, 2.06)	>100 (<0.01, >100)	Tinzaparin	1.16 (0.59, 2.26)	1.26 (0.638, 2.52)	1.49 (0.97, 2.31)
Heparin	0.672 (0.45, 1.01)	0.813 (0.414, 1.63)	>100 (<0.01, >100)	0.859 (0.442, 1.7)	Heparin	1.08 (0.561, 2.13)	1.28 (0.771, 2.15)
Aspirin	0.62 (0.364, 1.04)	0.749 (0.348, 1.6)	>100 (<0.01, >100)	0.792 (0.398, 1.57)	0.922 (0.469, 1.78)	Aspirin	1.18 (0.7, 1.99)
Warfarin	0.525 (0.379, 0.717)	0.635 (0.333, 1.2)	>100 (<0.01, >100)	0.671 (0.433, 1.03)	0.781 (0.464, 1.3)	0.846 (0.503, 1.43)	Warfarin
Placebo	0.328 (0.232, 0.465)	0.396 (0.217, 0.725)	>100 (<0.01, >100)	0.418 (0.22, 0.796)	0.488 (0.285, 0.827)	0.529 (0.286, 0.986)	0.625 (0.39, 1)
Enoxaparin+GCS	<0.01 (<0.01, 0.0112)	<0.01 (<0.01, 0.0136)	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.0135)	<0.01 (<0.01, 0.0166)	<0.01 (<0.01, 0.017)	<0.01 (<0.01, 0.0209)

	Placebo	Enoxaparin+GCS
Rivaroxaban	14.4 (5, 52.8)	>100 (>100, >100)
Aspirin+VFP	10.8 (3.4, 36.5)	>100 (>100, >100)
Fondaparinux	7.54 (4.42, 12.8)	>100 (>100, >100)
Edoxaban	6.39 (3.77, 11)	>100 (>100, >100)
Apixaban	5.75 (3.52, 9.5)	>100 (>100, >100)
Darexaban	5.49 (2.58, 12.7)	>100 (>100, >100)
Dabigatran	5.38 (3.21, 9.03)	>100 (>100, >100)
Enoxaparin+IPC	5.23 (1.5, 20)	>100 (>100, >100)
IPC	4.88 (1.75, 13.5)	>100 (>100, >100)
FXIASO	3.95 (1.81, 8.58)	>100 (>100, >100)
Aspirin+IPC	3.95 (0.925, 18)	>100 (>100, >100)
Semuloparin	3.68 (2.16, 6.3)	>100 (>100, >100)
Enoxaparin+VFP	0.0168 (<0.01, >100)	>100 (<0.01, >100)
Edoxaban+VFP	3.01 (1.06, 8.59)	>100 (87.4, >100)
Enoxaparin	3.05 (2.15, 4.31)	>100 (89, >100)
VFP	2.53 (1.38, 4.6)	>100 (73.3, >100)
Flexion	<0.01 (<0.01, >100)	>100 (<0.01, >100)
Tinzaparin	2.39 (1.26, 4.55)	>100 (74.1, >100)
Heparin	2.05 (1.21, 3.51)	>100 (60.2, >100)
Aspirin	1.89 (1.01, 3.49)	>100 (58.8, >100)
Warfarin	1.6 (0.998, 2.56)	>100 (47.8, >100)
Placebo	Placebo	>100 (30, >100)
Enoxaparin+GCS	<0.01 (<0.01, 0.0333)	Enoxaparin+GCS

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: DVT = deep vein thrombosis, GCS = graduated compression stocking, IPC = intermittent pneumatic compression, VFP = venous foot pump.

Table G7. Network meta-analysis pairwise results: Total knee replacement, intervention class comparisons of major bleeding

	VKA	LMWH	UFH	Placebo	DTI	FXIi	FXaI+ Mechanical	FXaI
VKA	VKA	2.05 (0.861, 5.28)	2.07 (0.233, 19.4)	2.31 (0.411, 13.4)	2.32 (0.779, 8.5)	642 (<0.01, >100)	3.37 (0.33, 38.6)	3.1 (1.04, 11.3)
LMWH	0.488 (0.189, 1.16)	LMWH	1 (0.136, 7.81)	1.11 (0.251, 5.2)	1.13 (0.56, 2.67)	322 (<0.01, >100)	1.62 (0.189, 15.4)	1.51 (0.748, 3.62)
UFH	0.482 (0.0515, 4.3)	0.997 (0.128, 7.35)	UFH	1.11 (0.087, 14.1)	1.13 (0.135, 10.2)	320 (<0.01, >100)	1.62 (0.0834, 33.5)	1.52 (0.178, 13.7)
Placebo	0.432 (0.0749, 2.44)	0.9 (0.192, 3.99)	0.903 (0.071, 11.5)	Placebo	1.02 (0.222, 5.02)	303 (<0.01, >100)	1.45 (0.107, 21.2)	1.36 (0.259, 7.64)
DTI	0.431 (0.118, 1.28)	0.884 (0.374, 1.78)	0.883 (0.0979, 7.42)	0.982 (0.199, 4.5)	DTI	288 (<0.01, >100)	1.43 (0.14, 14.5)	1.33 (0.464, 3.97)
FXIi	0.00156 (<0.01, >100)	0.00311 (<0.01, >100)	0.00313(<0.01, >100)	0.0033 (<0.01, >100)	0.00347 (<0.01, >100)	FXIi	0.00498 (<0.01, >100)	0.00473 (<0.01, >100)
FXaI+ Mechanical	0.297 (0.0259, 3.03)	0.617 (0.0649, 5.3)	0.618 (0.0299, 12)	0.687 (0.0473, 9.36)	0.699 (0.0688, 7.13)	201(<0.01, >100)	FXaI+ Mechanical	0.937 (0.12, 7.35)
FXaI	0.322 (0.0886, 0.965)	0.664 (0.276, 1.34)	0.658 (0.0732, 5.63)	0.735 (0.131, 3.86)	0.751 (0.252, 2.16)	211 (<0.01, >100)	1.07 (0.136, 8.36)	FXaI

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Abbreviations: DTI = direct thrombin inhibitor, FXaI = factor Xa inhibitor, FXIi = factor XI inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin, VKA = vitamin K antagonist

Table G8. Network meta-analysis pairwise results: Total knee replacement, specific intervention comparisons of major bleeding

	FXIASO	Warfarin	Eribaxaban	Apixaban	TAK442	Semuloparin	Heparin	Enoxaparin
FXIASO	FXIASO	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Warfarin	<0.01 (<0.01, >100)	Warfarin	0.81 (0.0198, 10.4)	1.06 (0.258, 4.41)	1.03 (0.088, 9.09)	1.19 (0.164, 8.13)	1.71 (0.212, 13)	1.66 (0.681, 4.55)
Eribaxaban	<0.01 (<0.01, >100)	1.23 (0.0963, 50.6)	Eribaxaban	1.33 (0.0951, 55.6)	1.3 (0.0494, 73.7)	1.49 (0.0777, 76.7)	2.2 (0.0963, 110)	2.02 (0.194, 74.5)
Apixaban	<0.01 (<0.01, >100)	0.945 (0.227, 3.88)	0.753 (0.018, 10.5)	Apixaban	0.965 (0.0811, 9.05)	1.12 (0.146, 8.24)	1.61 (0.189, 13.5)	1.57 (0.563, 4.64)
TAK442	<0.01 (<0.01, >100)	0.972 (0.11, 11.4)	0.77 (0.0136, 20.3)	1.04 (0.111, 12.3)	TAK442	1.17 (0.0811, 19.2)	1.67 (0.109, 29.2)	1.62 (0.232, 15.7)
Semuloparin	<0.01 (<0.01, >100)	0.841 (0.123, 6.08)	0.673 (0.013, 12.9)	0.889 (0.121, 6.83)	0.853 (0.052, 12.3)	Semuloparin	1.43 (0.118, 17.3)	1.4 (0.264, 8.17)
Heparin	<0.01 (<0.01, >100)	0.584 (0.0767, 4.71)	0.454 (0.00907, 10.4)	0.622 (0.0743, 5.29)	0.6 (0.0342, 9.13)	0.697 (0.0578, 8.51)	Heparin	0.987 (0.161, 6.49)
Enoxaparin	<0.01 (<0.01, >100)	0.604 (0.22, 1.47)	0.494 (0.0134, 5.16)	0.637 (0.216, 1.78)	0.616 (0.0638, 4.31)	0.714 (0.122, 3.78)	1.01 (0.154, 6.21)	Enoxaparin
Dabigatran	<0.01 (<0.01, >100)	0.543 (0.157, 1.62)	0.438 (0.0108, 5.14)	0.572 (0.155, 1.91)	0.554 (0.0515, 4.26)	0.64 (0.0956, 3.76)	0.918 (0.123, 6.25)	0.904 (0.447, 1.71)
Placebo	<0.01 (<0.01, >100)	0.431 (0.0691, 2.54)	0.338 (0.0069, 5.98)	0.457 (0.0704, 2.89)	0.437 (0.0286, 5.43)	0.518 (0.0479, 4.86)	0.729 (0.0657, 7.5)	0.731 (0.153, 3.19)
Tinzaparin	<0.01 (<0.01, >100)	0.299 (0.0579, 1.22)	0.227 (0.00431, 4.77)	0.312 (0.0362, 2.31)	0.298 (0.0171, 4.01)	0.345 (0.0271, 3.96)	0.499 (0.0349, 6.11)	0.492 (0.0752, 2.8)
Edoxaban+VFP	<0.01 (<0.01, >100)	0.0964 (0.00206, 2.05)	0.0712 (0.000493, 3.37)	0.103 (0.00218, 2.3)	0.0963 (0.00125, 3.5)	0.113 (0.00193, 3.31)	0.163 (0.00257, 5.48)	0.165 (0.00393, 2.97)
Edoxaban	<0.01 (<0.01, >100)	0.104 (0.00354, 1.16)	0.0758 (0.000732, 2.14)	0.112 (0.00365, 1.29)	0.102 (0.00225, 2.18)	0.124 (0.00303, 2.07)	0.177 (0.00427, 3.24)	0.181 (0.00665, 1.58)
Fondaparinux	<0.01 (<0.01, >100)	0.0405 (0.00184, 0.32)	0.029 (0.000319, 0.745)	0.0424 (0.00189, 0.385)	0.0381 (0.00119, 0.638)	0.047 (0.00149, 0.589)	0.0665 (0.00203, 0.981)	0.0685 (0.00373, 0.438)
Darexaban	<0.01 (<0.01, >100)	<0.01 (<0.01, 0.119)	<0.01 (<0.01, 0.135)	<0.01 (<0.01, 0.13)	<0.01 (<0.01, 0.143)	<0.01 (<0.01, 0.157)	<0.01 (<0.01, 0.24)	<0.01 (<0.01, 0.191)

	Dabigatran	Placebo	Tinzaparin	Edoxaban+VFP	Edoxaban	Fondaparinux	Darexaban
FXIASO	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)	>100 (<0.01, >100)
Warfarin	1.84 (0.619, 6.37)	2.32 (0.393, 14.5)	3.35 (0.821, 17.3)	10.4 (0.488, 485)	9.58 (0.864, 283)	24.7 (3.13, 543)	>100 (8.4, >100)
Eribaxaban	2.29 (0.195, 92.3)	2.96 (0.167, 145)	4.41 (0.21, 232)	14 (0.297, 2.03e+03)	13.2 (0.468, 1.37e+03)	34.5 (1.34, 3.13e+03)	>100 (7.39, >100)
Apixaban	1.75 (0.524, 6.47)	2.19 (0.346, 14.2)	3.2 (0.434, 27.6)	9.71 (0.434, 459)	8.94 (0.776, 274)	23.6 (2.6, 530)	>100 (7.66, >100)
TAK442	1.8 (0.235, 19.4)	2.29 (0.184, 35)	3.35 (0.249, 58.4)	10.4 (0.286, 797)	9.77 (0.46, 444)	26.2 (1.57, 839)	>100 (7.01, >100)
Semuloparin	1.56 (0.266, 10.5)	1.93 (0.206, 20.9)	2.9 (0.252, 36.9)	8.84 (0.302, 517)	8.09 (0.484, 331)	21.3 (1.7, 669)	>100 (6.35, >100)
Heparin	1.09 (0.16, 8.1)	1.37 (0.133, 15.2)	2 (0.164, 28.6)	6.13 (0.183, 390)	5.65 (0.308, 234)	15 (1.02, 493)	>100 (4.16, >100)
Enoxaparin	1.11 (0.586, 2.24)	1.37 (0.313, 6.56)	2.03 (0.357, 13.3)	6.05 (0.336, 254)	5.52 (0.634, 150)	14.6 (2.28, 268)	>100 (5.24, >100)
Dabigatran	Dabigatran	1.24 (0.268, 5.85)	1.83 (0.273, 13.3)	5.45 (0.278, 239)	5.03 (0.501, 140)	13.3 (1.77, 261)	>100 (4.83, >100)
Placebo	0.809 (0.171, 3.73)	Placebo	1.47 (0.14, 15.9)	4.53 (0.164, 231)	4.15 (0.27, 130)	11.1 (0.859, 263)	>100 (3.33, >100)
Tinzaparin	0.547 (0.075, 3.66)	0.682 (0.063, 7.16)	Tinzaparin	3.06 (0.091, 182)	2.89 (0.146, 106)	7.39 (0.533, 224)	>100 (2.03, >100)
Edoxaban+VFP	0.183 (0.00419, 3.59)	0.221 (0.00433, 6.09)	0.327 (0.00551, 11)	Edoxaban+VFP	0.953 (0.148, 6.02)	2.56 (0.0383, 147)	>100 (0.639, >100)
Edoxaban	0.199 (0.00713, 2)	0.241 (0.0077, 3.71)	0.347 (0.00947, 6.84)	1.05 (0.166, 6.77)	Edoxaban	2.67 (0.0651, 97.4)	>100 (0.801, >100)
Fondaparinux	0.0751 (0.00383, 0.566)	0.0901 (0.0038, 1.16)	0.135 (0.00446, 1.88)	0.391 (0.00679, 26.1)	0.375 (0.0103, 15.4)	Fondaparinux	>100 (0.248, >100)
Darexaban	<0.01 (<0.01, 0.207)	<0.01 (<0.01, 0.301)	<0.01 (<0.01, 0.492)	<0.01 (<0.01, 1.57)	<0.01 (<0.01, 1.25)	<0.01 (<0.01, 4.04)	Darexaban

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: GCS = graduated compression stocking, IPC = intermittent pneumatic compression, VFP = venous foot pump.

Table G9. Network meta-analysis pairwise results: Hip fracture surgery, intervention class comparisons of total DVT

	UFH	FXaI	LMWH	Placebo
UFH	UFH	1.28 (0.35, 5.3)	3.28 (0.967, 12.4)	8.78 (2.04, 41.2)
FXaI	0.783 (0.189, 2.85)	FXaI	2.57 (1.51, 4.09)	6.84 (2.86, 16.7)
LMWH	0.305 (0.0809, 1.03)	0.389 (0.245, 0.66)	LMWH	2.67 (1.22, 6.13)
Placebo	0.114 (0.0243, 0.49)	0.146 (0.06, 0.349)	0.375 (0.163, 0.817)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: DVT = deep vein thrombosis, FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, UFH = unfractionated heparin

Table G10. Network meta-analysis pairwise results: Hip fracture surgery, specific intervention comparisons of total DVT

	Heparin	Fondaparinux	Dalteparin	Semuloparin	Enoxaparin	Edoxaban	Placebo
Heparin	Heparin	2.58 (0.494, 14.2)	3.26 (0.96, 11.9)	5.35 (0.987, 31)	7.36 (1.51, 38.8)	19.1 (0.97, 829)	13.6 (2.77, 70.2)
Fondaparinux	0.388 (0.0705, 2.02)	Fondaparinux	1.27 (0.422, 3.72)	2.06 (1.02, 4.44)	2.84 (1.78, 4.71)	7.08 (0.591, 240)	5.19 (2.07, 13.8)
Dalteparin	0.306 (0.0837, 1.04)	0.789 (0.269, 2.37)	Dalteparin	1.63 (0.525, 5.29)	2.25 (0.834, 6.36)	5.7 (0.404, 198)	4.12 (1.55, 11.3)
Semuloparin	0.187 (0.0322, 1.01)	0.486 (0.225, 0.981)	0.612 (0.189, 1.91)	Semuloparin	1.38 (0.79, 2.38)	3.4 (0.285, 117)	2.52 (0.888, 7.3)
Enoxaparin	0.136 (0.0258, 0.662)	0.352 (0.212, 0.561)	0.444 (0.157, 1.2)	0.725 (0.42, 1.27)	Enoxaparin	2.45 (0.219, 80.7)	1.82 (0.748, 4.57)
Edoxaban	0.0523 (0.00121, 1.03)	0.141 (0.00417, 1.69)	0.176 (0.00504, 2.48)	0.294 (0.00854, 3.51)	0.408 (0.0124, 4.57)	Edoxaban	0.74 (0.0204, 9.79)
Placebo	0.0738 (0.0142, 0.362)	0.193 (0.0726, 0.484)	0.242 (0.0885, 0.645)	0.397 (0.137, 1.13)	0.548 (0.219, 1.34)	1.35 (0.102, 48.9)	Placebo

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: DVT = deep vein thrombosis.

Table G11. Network meta-analysis pairwise results: Hip fracture surgery, intervention class comparisons of major bleeding

	Antiplatelet	VKA	Placebo	LMWH	FXaI
Antiplatelet	Antiplatelet	7.27 (0.932, 279)	7.63 (0.912, 280)	>100 (4.1, >100)	>100 (4.48, >100)
VKA	0.138 (0.00359, 1.07)	VKA	1.04 (0.242, 4.43)	>100 (0.722, >100)	>100 (0.827, >100)
Placebo	0.131 (0.00357, 1.1)	0.959 (0.226, 4.13)	Placebo	>100 (0.802, >100)	>100 (0.904,> 100)
LMWH	<0.01 (<0.01, 0.244)	<0.01 (<0.01, 1.39)	<0.01 (<0.01, 1.25)	LMWH	1.06 (0.512, 2.39)
FXaI	<0.01 (<0.01, 0.223)	<0.01 (<0.01, 1.21)	<0.01 (<0.01, 1.11)	0.946 (0.419, 1.95)	FXaI

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all classes. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.
Abbreviations: FXaI = factor Xa inhibitor, LMWH = low molecular weight heparin, VKA = vitamin K antagonist

Table G12. Network meta-analysis pairwise results: Hip fracture surgery, specific intervention comparisons of major bleeding

	Aspirin	Warfarin	Placebo	Dalteparin	Edoxaban	Enoxaparin	Fondaparinux	Semuloparin
Aspirin	Aspirin	7.35 (0.864, >100)	7.62 (0.87, >100)	>100 (2.05, >100)	>100 (2.27, >100)	>100 (9.87, >100)	>100 (11.3, >100)	>100 (14.5, >100)
Warfarin	0.136 (<0.01, 1.16)	Warfarin	1.04 (0.233, 4.43)	>100 (0.331, >100)	>100 (0.329, >100)	>100 (1.56, >100)	>100 (1.79, >100)	>100 (2.44, >100)
Placebo	0.131 (<0.01, 1.15)	0.962 (0.226, 4.29)	Placebo	>100 (0.358, >100)	>100 (0.383, >100)	>100 (1.71, >100)	>100 (1.99, >100)	>100 (2.71, >100)
Dalteparin	<0.01 (<0.01, 0.489)	<0.01 (<0.01, 3.02)	<0.01 (<0.01, 2.79)	Dalteparin	1.3 (0.0135, 173)	2.47 (0.182, 79.9)	2.86 (0.189, 98.4)	4.6 (0.214, 209)
Edoxaban	<0.01 (<0.01, 0.44)	<0.01 (<0.01, 3.04)	<0.01 (<0.01, 2.61)	0.772 (0.00579, 74.3)	Edoxaban	2.06 (0.0525, 85.7)	2.32 (0.056, 108)	3.78 (0.0676, 220)
Enoxaparin	<0.01 (<0.01, 0.101)	<0.01 (<0.01, 0.643)	<0.01 (<0.01, 0.586)	0.405 (0.0125, 5.49)	0.486 (0.0117, 19)	Enoxaparin	1.13 (0.516, 2.89)	1.8 (0.374, 10.2)
Fondaparinux	<0.01 (<0.01, 0.0889)	<0.01 (<0.01, 0.559)	<0.01 (<0.01, 0.502)	0.35 (0.0102, 5.3)	0.431 (0.00927, 17.8)	0.888 (0.346, 1.94)	Fondaparinux	1.61 (0.251, 10.6)
Semuloparin	<0.01 (<0.01, 0.0688)	<0.01 (<0.01, 0.41)	<0.01 (<0.01, 0.368)	0.217 (0.00479, 4.68)	0.264 (0.00455, 14.8)	0.554 (0.0985, 2.67)	0.621 (0.0948, 3.98)	Semuloparin

Pairwise meta-analysis results of odds ratio (with 95% credible interval) from network meta-analysis comparing all interventions. Values above diagonal compare row with column such that estimates >1 favor the column class. Values below the diagonal compare the column with the row such that estimates >1 favor the row class.

Appendix H. Network Topologies for Symptomatic Deep Vein Thrombosis and Total Pulmonary Embolism

Figure H1. Network for total hip replacement, intervention class comparisons of symptomatic DVT

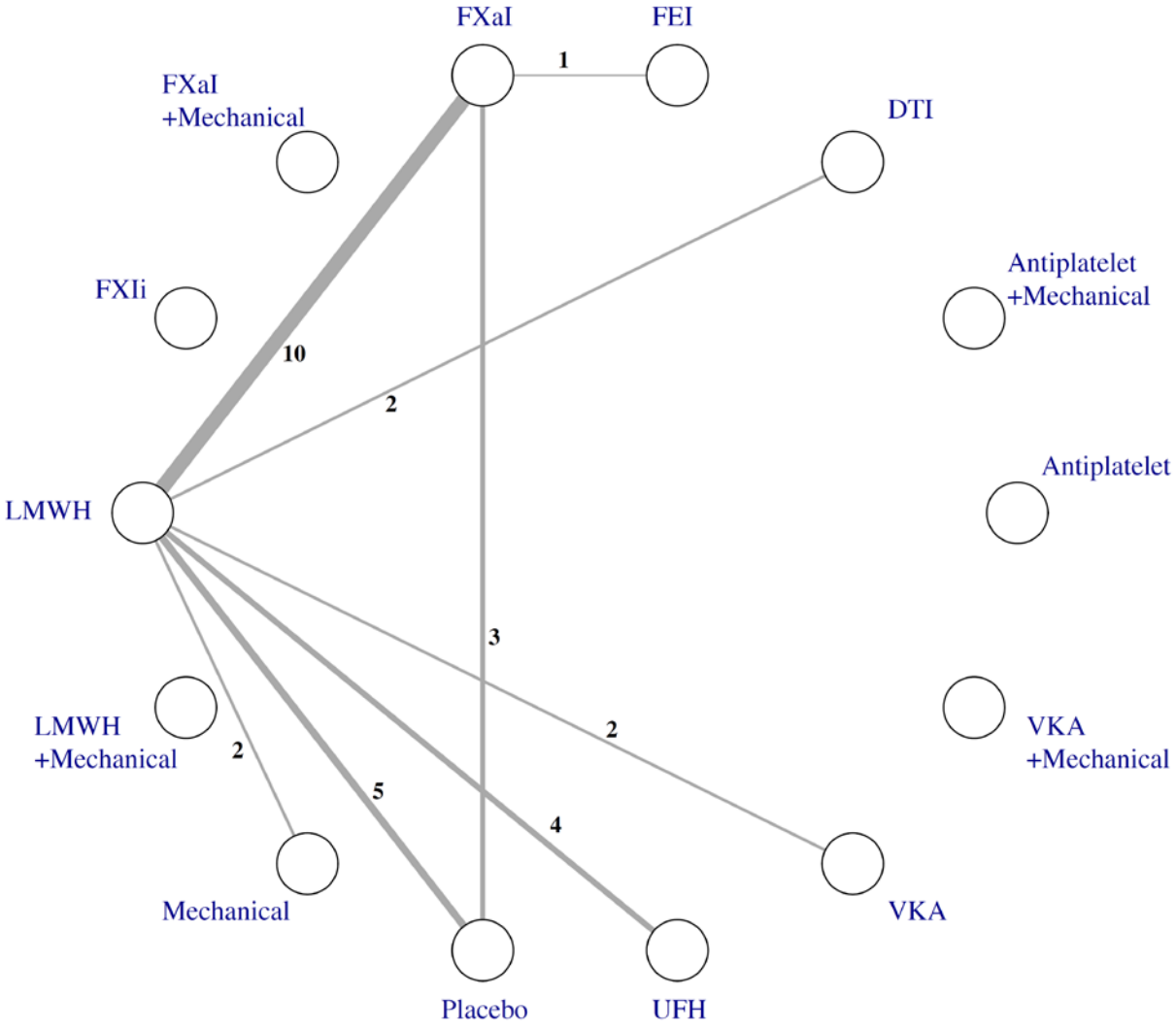

Figure H2. Network for total hip replacement, specific intervention comparisons of symptomatic DVT

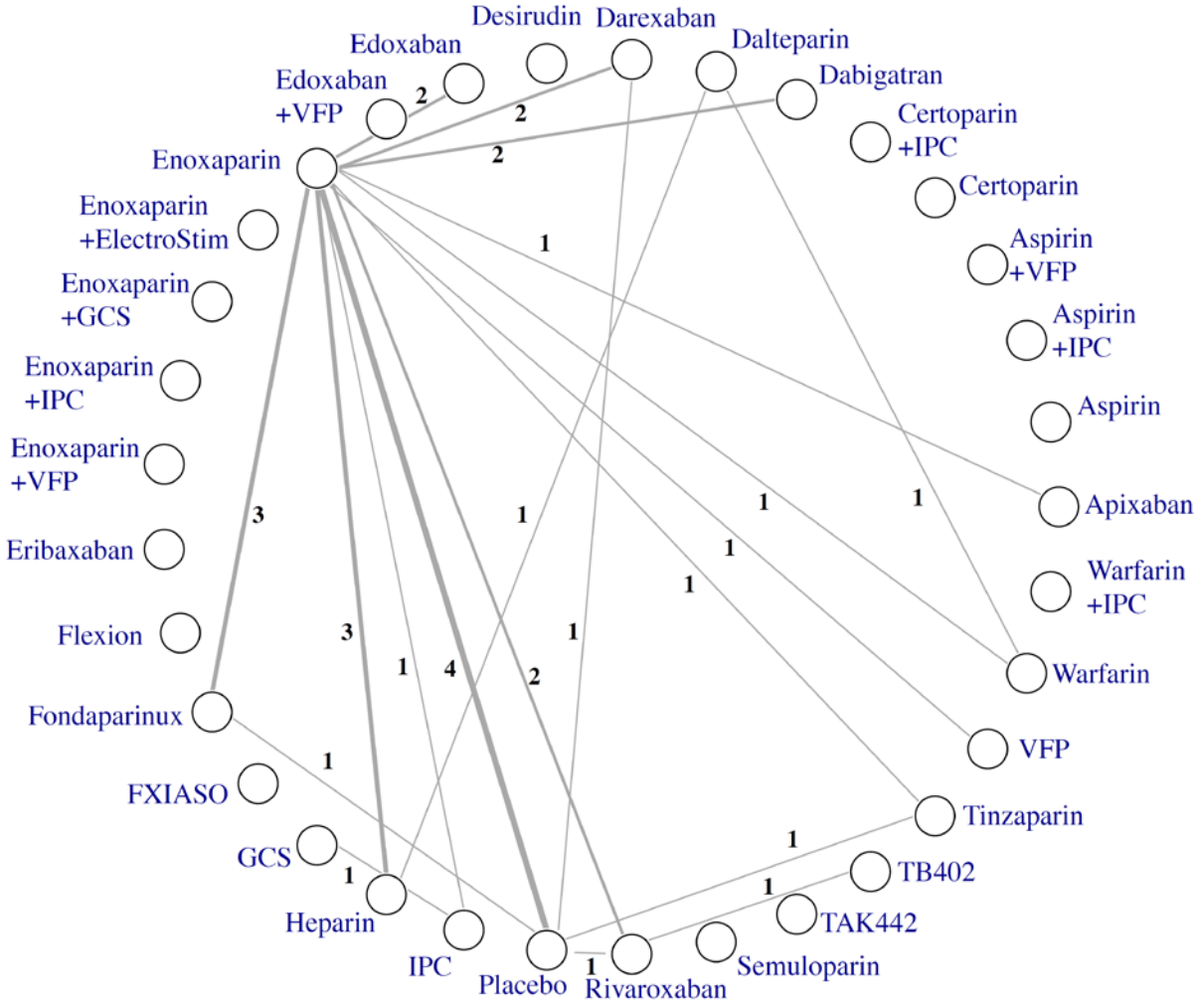

Figure H3. Network for total hip replacement, intervention class comparisons of total PE

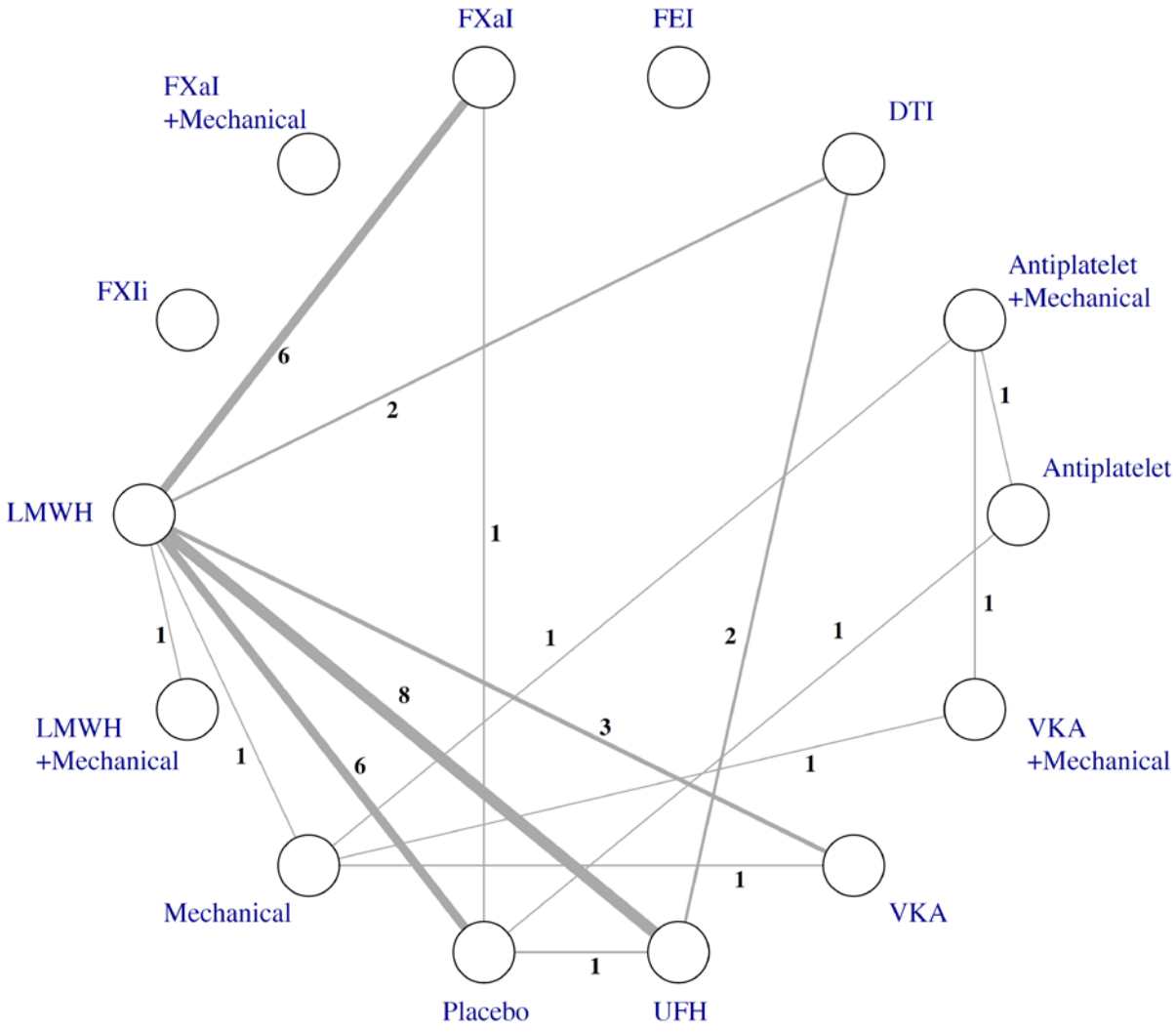

Figure H4. Network for total hip replacement, specific intervention comparisons of total PE

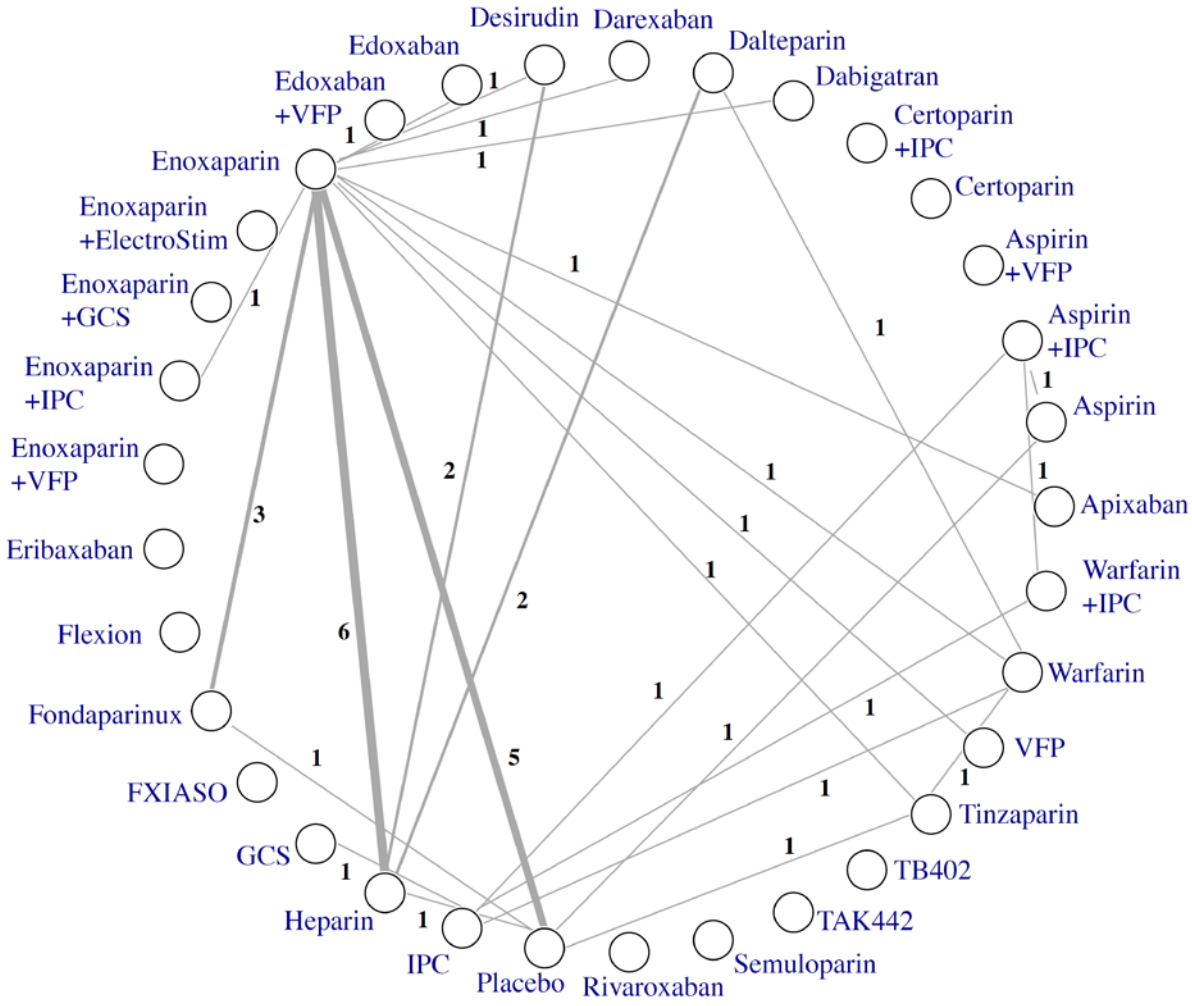

Figure H5. Network for total knee replacement, intervention class comparisons of symptomatic DVT

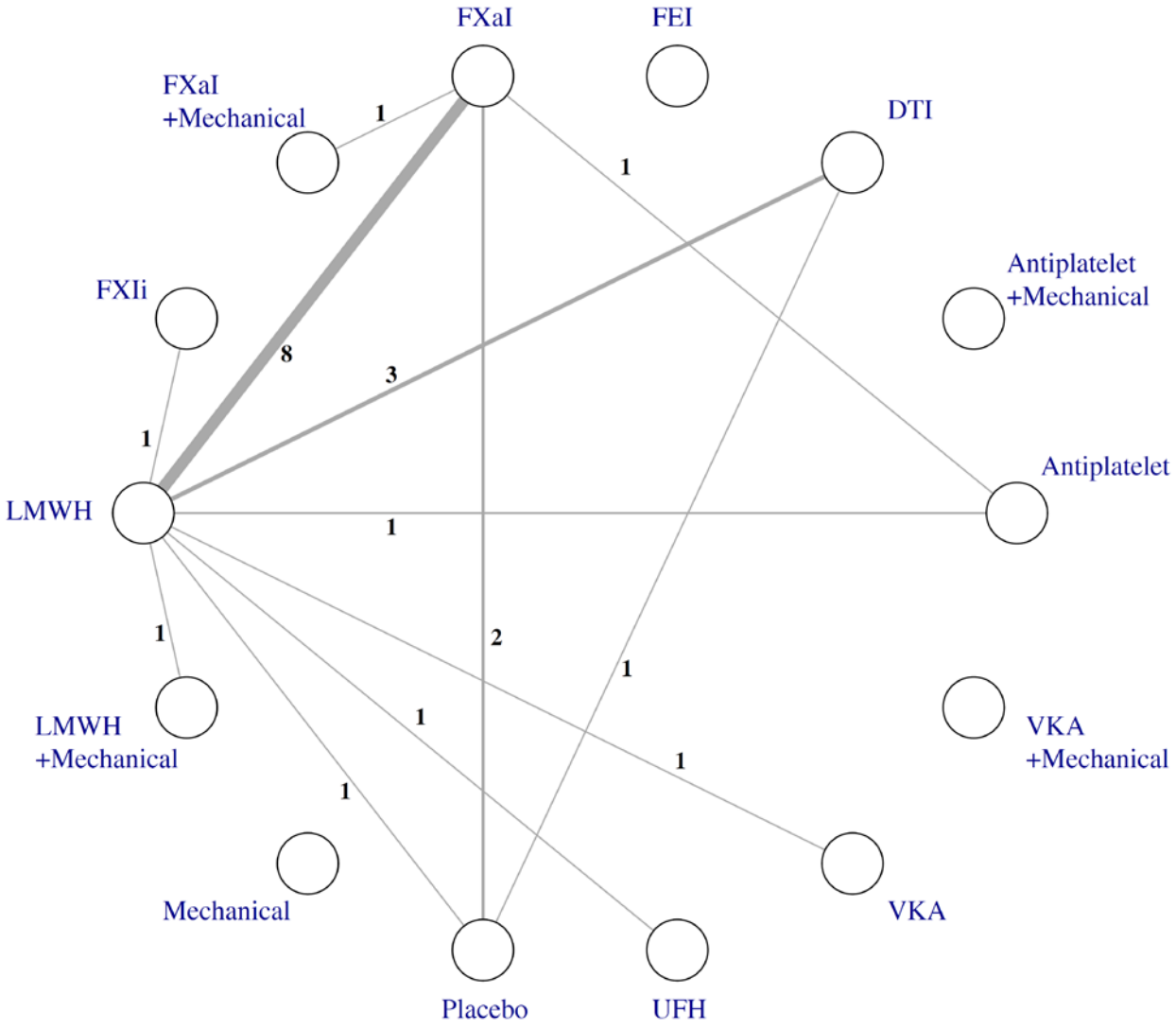

Figure H6. Network for total knee replacement, specific intervention comparisons of symptomatic DVT

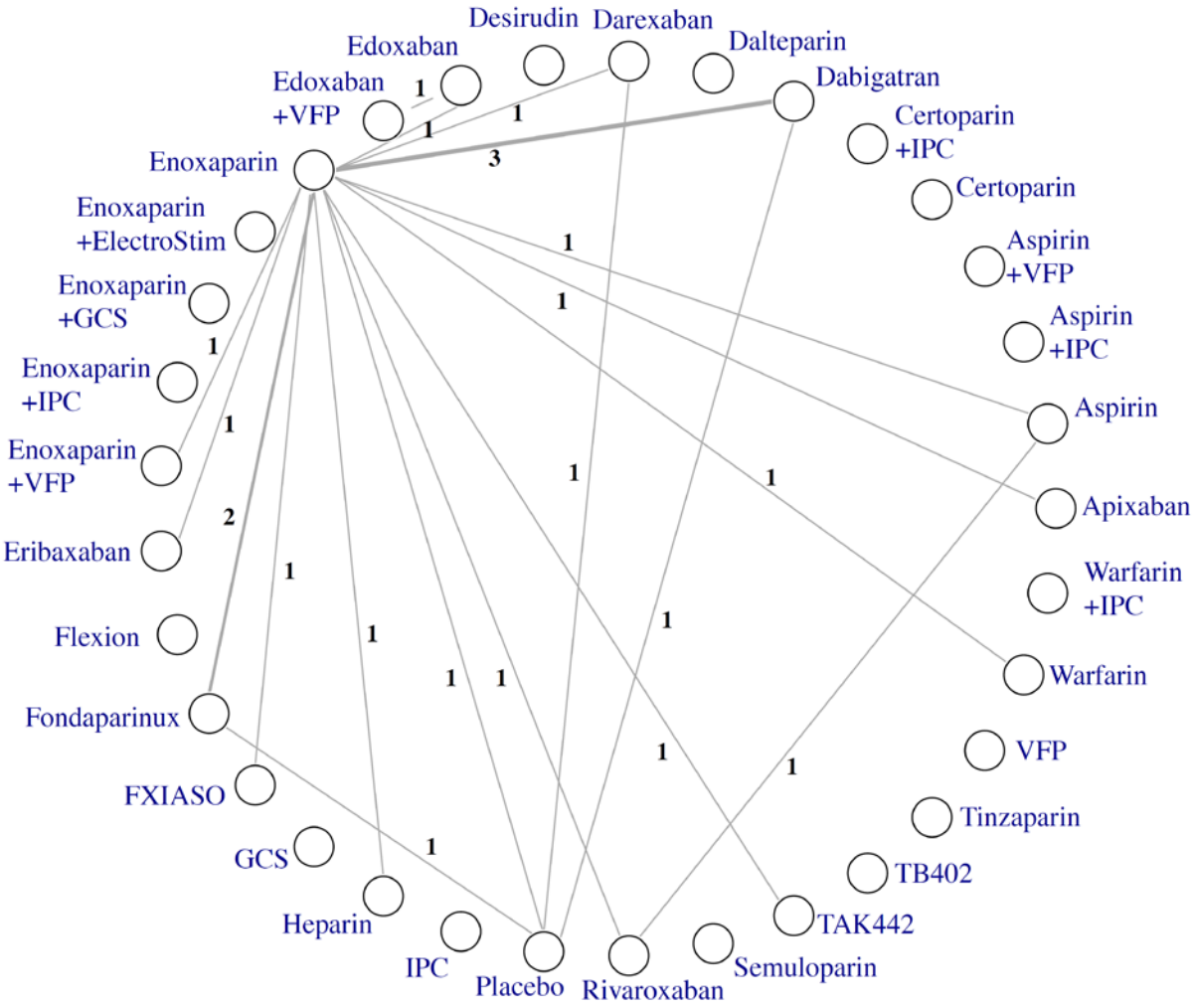

Figure H7. Network for total knee replacement, intervention class comparisons of total PE

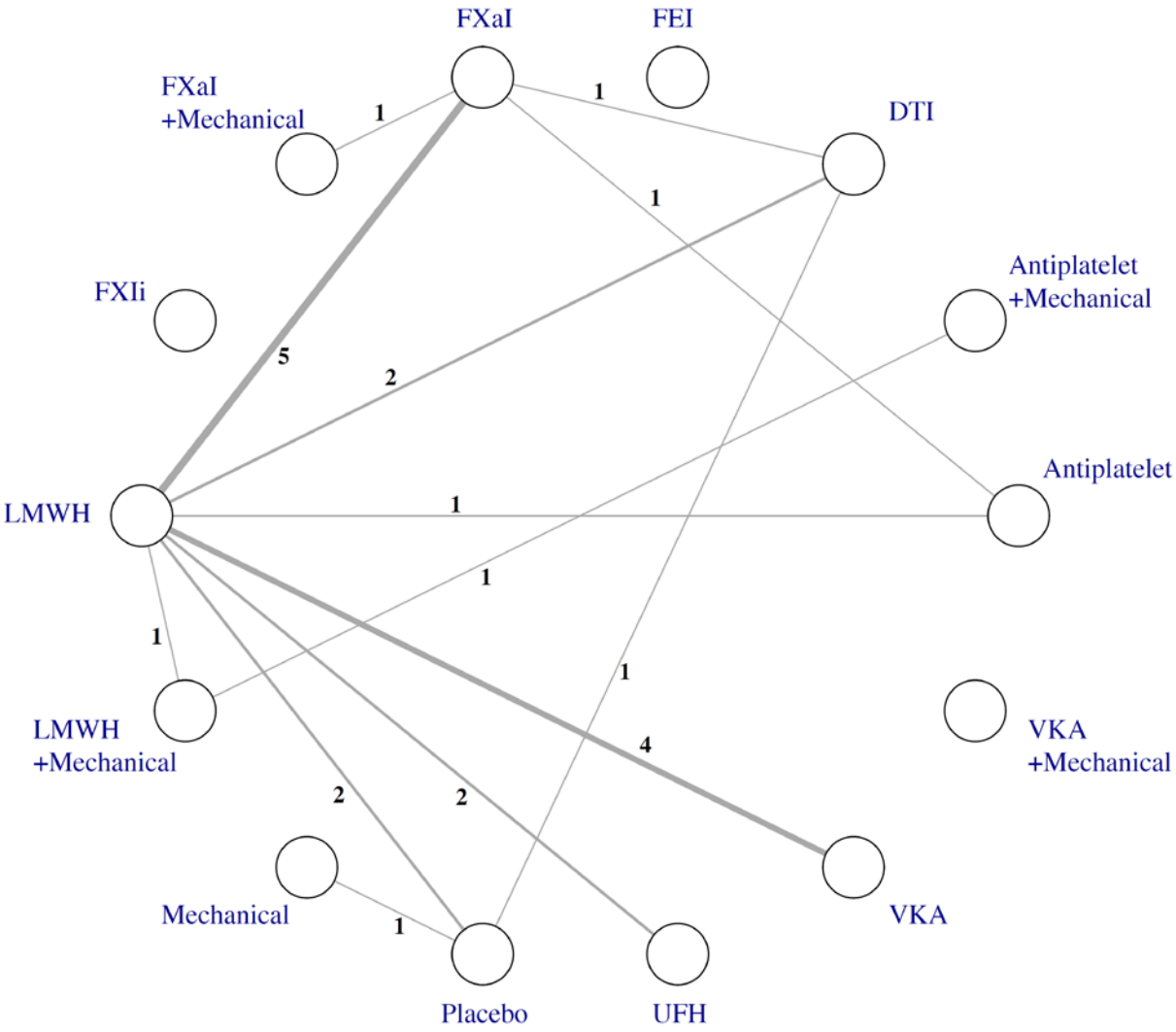

Figure H8. Network for total knee replacement, specific intervention comparisons of total PE

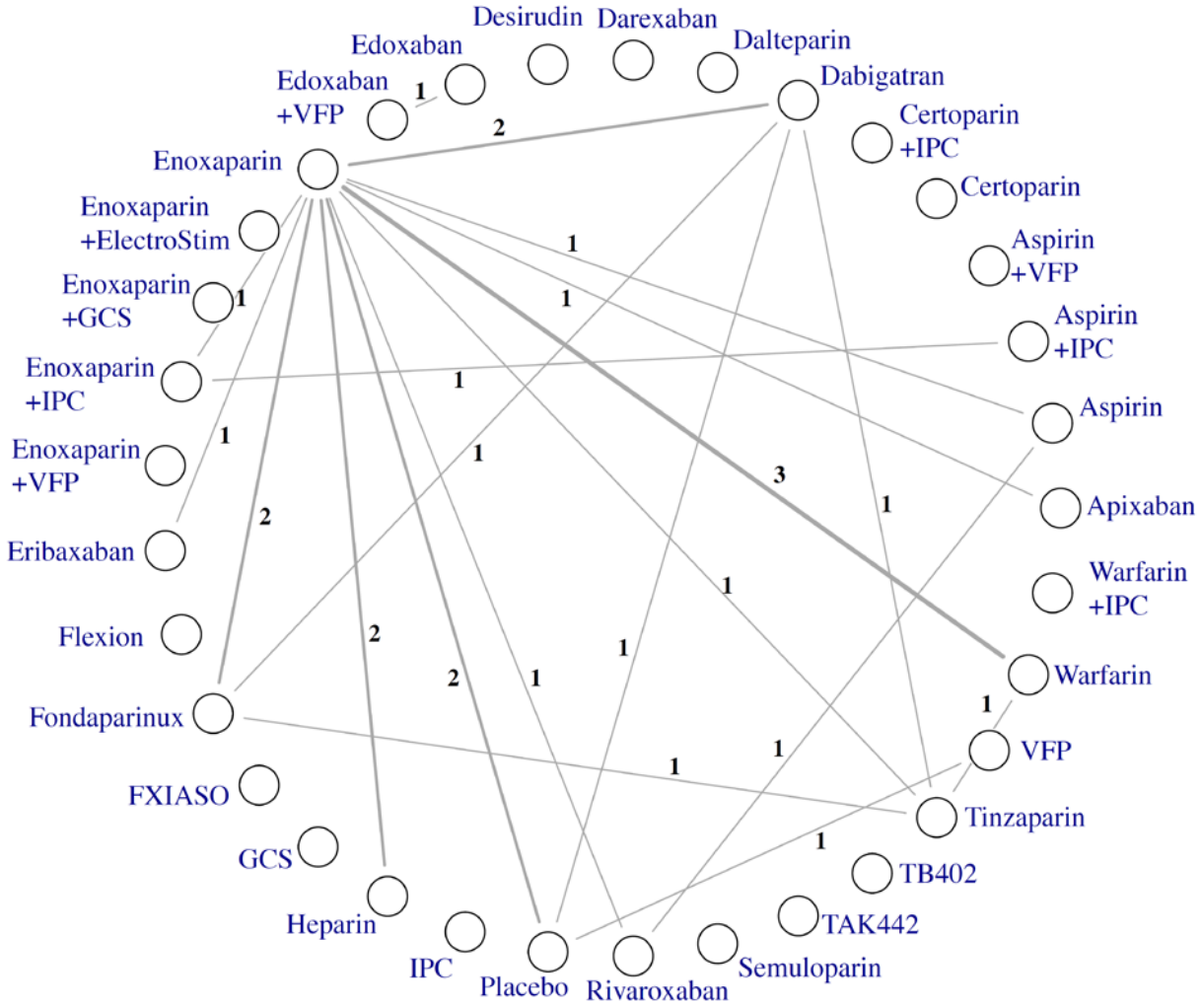

Figure H9. Network for hip fracture surgery, intervention class comparisons of symptomatic DVT

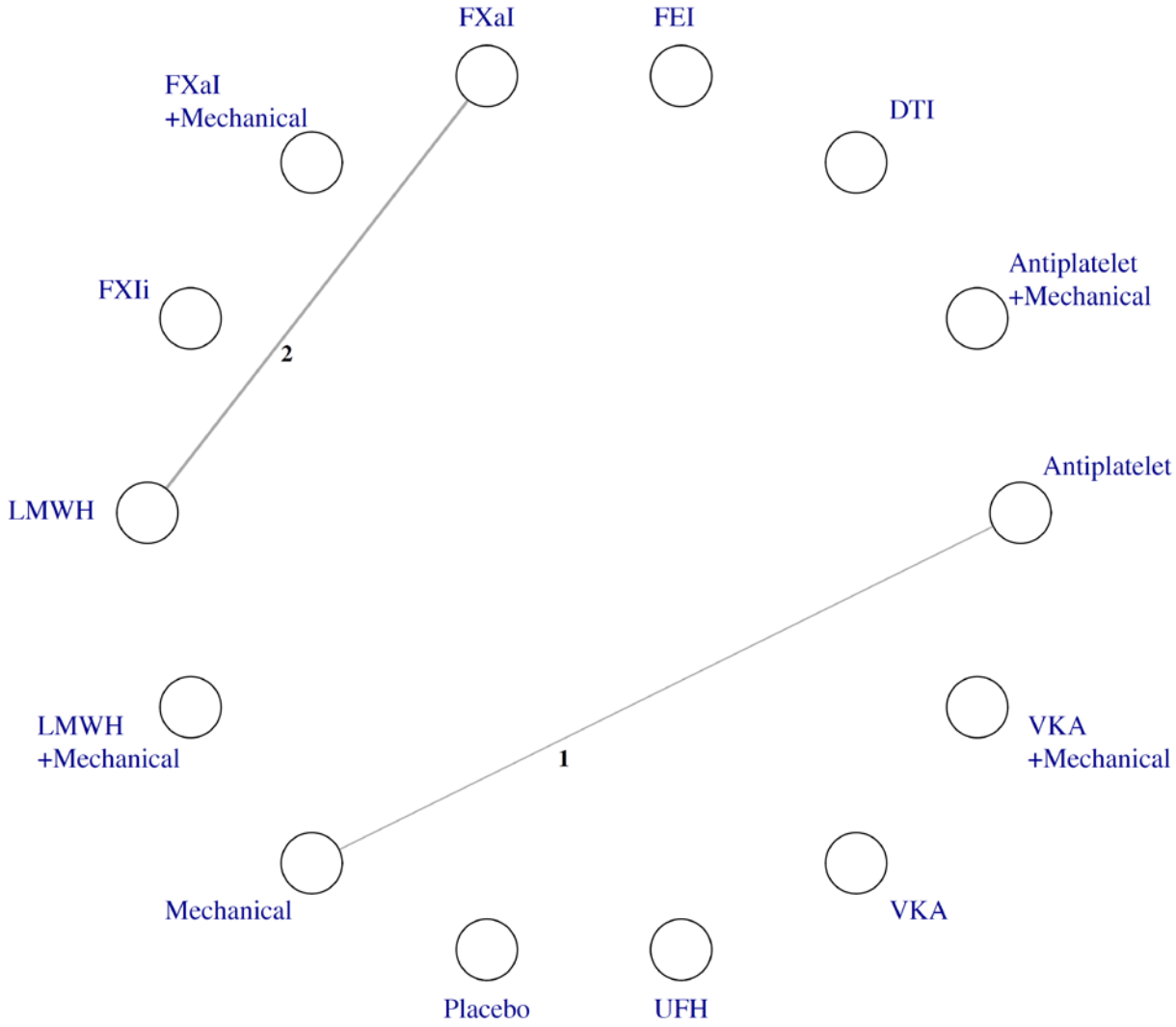

Figure H10. Network for hip fracture surgery, specific intervention comparisons of symptomatic DVT

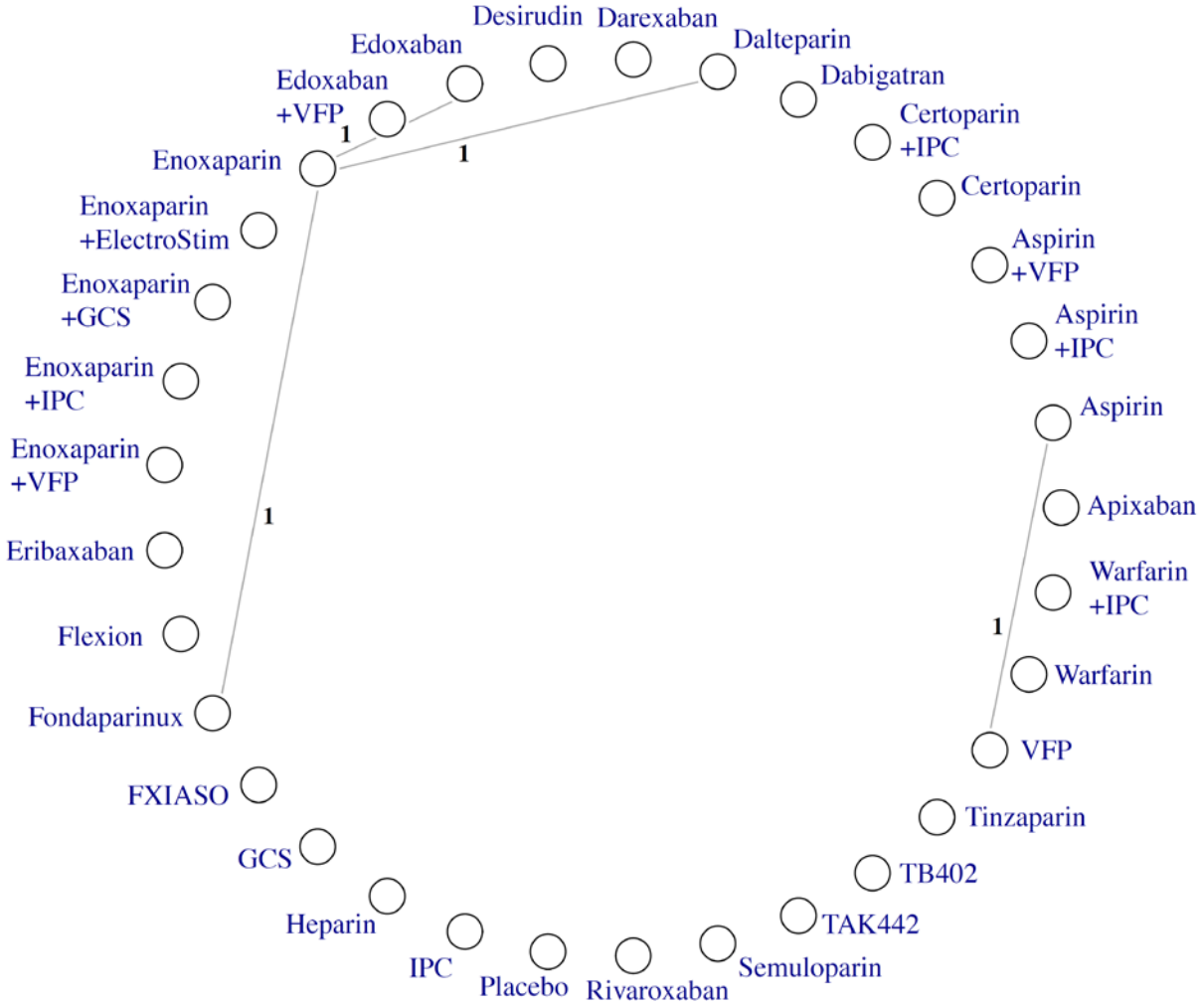

Figure H11. Network for hip fracture surgery, intervention class comparisons of total PE

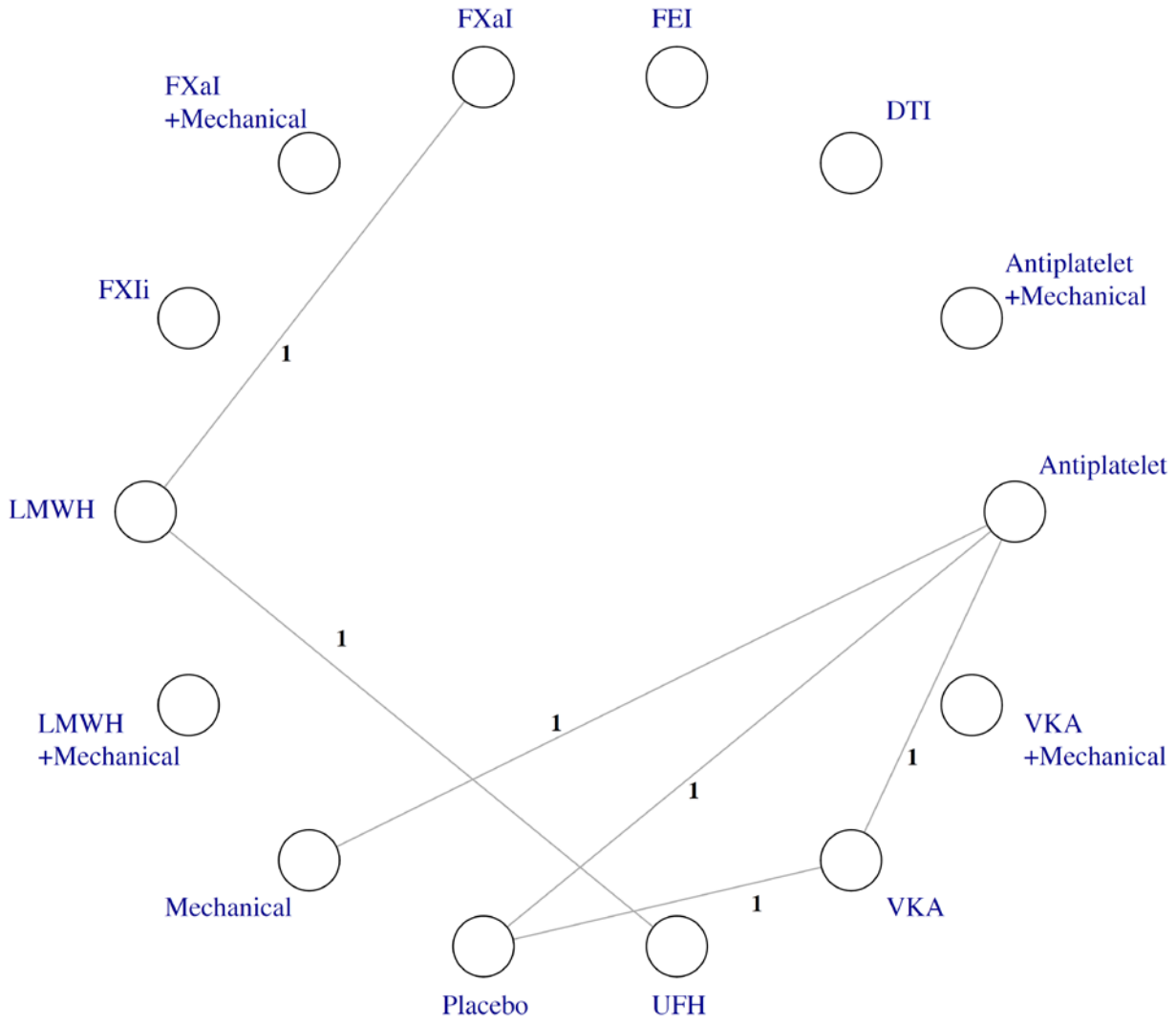

Figure H12. Network for hip fracture surgery, specific intervention comparisons of total PE