Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Venous Thromboembolism (VTE) Prophylaxis in Orthopedic Surgery

I. Background and Objectives for the Systematic Review

Background

Major orthopedic surgery (total hip replacement [THR], total knee replacement [TKR] or hip fracture surgery [HFS]) carries a high risk of venous thromboembolism (VTE). Pulmonary embolism (PE) following orthopedic surgery is reported to be rare.[1] However, without prophylaxis, hospital-acquired deep venous thrombosis (DVT) has been estimated to occur in 40-60% of cases in the 7-14 days following surgery compared to 10-40% among medical or general surgical patients.[2] A variety of strategies to prevent VTE are available and with routine use, the rate of symptomatic VTE in patients within 3 months of surgery is 1.3-10%.[2]

The main limitation of pharmacologic VTE prophylaxis is the risk of bleeding. Major bleeding following THR and TKR is estimated to be 1-3%.[1] Determining the incidence of major bleeding with pharmacologic thromboprophylaxis is complicated by the variability in the definitions used in published literature and paucity of data in control patients. Additionally, complications such as post-operative bleeding and hematoma formation are considered risk factors for the development of early-onset prosthetic joint infections.[3,4] Re-operation 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.

Currently, the American Academy of Orthopedic Surgeons (AAOS)[1] and the American College of Chest Physicians (ACCP)[2] publish guidelines related to the prevention of VTE in patients undergoing orthopedic surgery. The AAOS guidelines address THR or TKR surgery, whereas the ACCP guidelines also address HFS, knee arthroscopy, elective spine surgery, and isolated lower-extremity injuries distal to the knee. Since surgical technique and post-operative management of patients who have undergone a total joint replacement have changed significantly, the AAOS guidelines only include studies performed after 1995 in the analysis of pharmacologic efficacy and safety. On the other hand, the orthopedic surgery section of the ACCP guidelines does not indicate limiting the literature search to more recent data. One disagreement between the two sets of guidelines is in the use of DVT as a surrogate marker for PE and as a valid endpoint to measure efficacy of thromboprophylaxis. Ideally a surrogate marker would be correlated with a final outcome and demonstrate that an intervention impacting the surrogate marker also predicts the effect on the clinical outcome of interest.[5,6] In order to select the most appropriate form of prophylaxis, the AAOS encourages practitioners to individually assess each patient's risk of PE and bleeding whereas the ACCP suggests VTE prophylaxis based on the type of orthopedic surgery

given the inherent risk of VTE with these procedures. The guidelines also differ in the pharmacologic regimens recommended for VTE prophylaxis (individual agent, initiation time, and duration of therapy) as well as the optimal use of mechanical methods of prophylaxis. Finally, the AAOS guidelines suggest recommendations for the use of inferior vena cava (IVC) filters as a means of VTE prophylaxis in certain clinical situations whereas the ACCP guidelines do not comment on this topic. The resulting differences between the recommendations set forth by these guidelines have the potential to cause confusion during daily clinical practice. Ultimately the AAOS and the ACCP have intentions to collaboratively construct guidelines for the prevention of VTE in orthopedic surgery.

Objective

To perform a comparative effectiveness review examining the benefits and harms associated with venous thromboembolism prophylaxis in patients undergoing major orthopedic surgery, other orthopedic surgery or arthroscopy.

II. The Key Questions

Key Questions

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

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

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

Question 4: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis [any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins (LMWH), injectable unfractionated heparin, injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists (VKAs)) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump)] compared to no thromboprophylaxis on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or

VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Question 5: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding? Classes include oral antiplatelet agents, injectable low molecular weight heparins (LMWH), injectable unfractionated heparin, injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists (VKAs), and mechanical interventions?

Question 6: In patients undergoing major orthopedic surgery (total hip and knee replacement, hip fracture surgery), what is the comparative efficacy of individual agents within classes (LMWH and mechanical devices) on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Question 7: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities vs. single modality on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Question 8: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared to thromboprophylaxis for 7-10 days on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-

operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Question 9: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter (IVC) placement compared to any external mechanical intervention on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding or IVC filter placement-associated insertion site thrombosis?

Question 10: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared to no thromboprophylaxis intervention on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Question 11: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (LMWH vs. unfractionated heparin vs. factor Xa antagonists vs. direct thrombin inhibitors) compared to mechanical interventions on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion), heparin-induced thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?

Summary of Revisions to Key Questions

Upon public comment, we more explicitly delineate that we are interested in therapy based on contemporary clinical practice and which “other orthopedic surgeries” are going to be evaluated. We added an additional category of surgical site bleeding and explicit inclusion criteria for which imaging procedures for DVT or PE would be

included. We changed “immune mediated heparin induced thrombocytopenia” to simply “Heparin Induced Thrombocytopenia”, and rearranged a few words within the questions to make the points more clear as suggested by reviewers.

While it was suggested, we did not add additional agents to KQ6 because this question is meant to allow a determination of intragroup comparative effectiveness and other classes do not have more than one FDA approved medication within the class. Some reviewers felt we should limit VTE events to symptomatic events while others did not feel this way. Since our report is meant to represent a broad constituency of clinicians (surgeons, hematologists, hospitalists, internists, physician’s assistants, pharmacists, and nurses), patients, and healthcare decision-makers, a broader definition was selected. Other reviewers wanted us to add additional endpoints or additional populations to the review which was outside the scope of our CER.

Population(s)

- Patients undergoing major orthopedic surgery (total knee or hip replacement, hip fracture surgery); patients undergoing major orthopedic surgery (total knee or hip replacement, hip fracture surgery) with known contraindications to antithrombotic agents; patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery.

Interventions

- Thromboprophylaxis with one or more agents within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins (LMWH), injectable unfractionated heparin, injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists (VKAs)) or one or more external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump); prolonged duration of thromboprophylaxis; vena cava filter placement. See Tables 1 through 3 for pharmacologic therapy, IVC filters, and mechanical devices, respectively.

Table 1. Pharmacologic Agents

Pharmacol-ogic Class	Generic (Name brand)	Manufacturer	FDA Approved Indication(s)
Antiplatelets	Aspirin	Various	Not applicable
	Clopidogrel (Plavix®)	Sanofi Aventis / Bristol-Myers Squibb	Recent myocardial infarction, recent stroke, or established peripheral arterial disease; acute coronary syndrome
	Ticlopidine (Ticlid®)	Hoffman-La Roche Inc.	Reduce the risk of thrombotic stroke in patients who have experience stroke precursors and in patients who have

			completed thrombotic stroke
Vitamin K Antagonists	Warfarin (Coumadin®)	Bristol-Myers Squibb	Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism; prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
Heparins	Heparin	Various	Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery or who, for other reasons, are at risk of developing thromboembolic disease; prophylaxis and treatment of pulmonary embolism; atrial fibrillation with embolization; diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation); prevention of clotting in arterial and cardiac surgery; prophylaxis and treatment of peripheral arterial embolism; anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures and in blood samples for laboratory purposes
Low-molecular Weight Heparins	Enoxaparin (Lovenox®)	Sanofi Aventis	Prophylaxis of deep vein thrombosis in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness; inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism; outpatient treatment of acute deep vein thrombosis without pulmonary embolism; prophylaxis of ischemic complications of unstable angina and non-Q wave myocardial infarction; treatment of acute ST-segment elevation myocardial infarction managed medically or with subsequent percutaneous coronary intervention
	Dalteparin (Fragmin®)	Eisai Inc.	Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction; prophylaxis of deep vein thrombosis in abdominal surgery, hip replacement surgery or medical patients with severely restricted mobility during acute illness; extended treatment of symptomatic venous thromboembolism to reduce the recurrence in patients with cancer
	Tinzaparin (Innohep®)	LEO Pharma Inc.	Treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium
Direct Thrombin Inhibitors	Argatroban (Argatroban®)	Pfizer	Prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary intervention.
	Bivalirudin (Angiomax®)	The Medicines Company	Anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; anticoagulant in patients undergoing

			percutaneous coronary intervention; for patients with, or at risk of, heparin-induced thrombocytopenia/heparin-induced thrombocytopenia and thrombosis syndrome undergoing percutaneous coronary intervention
	Dabigatran (Pradaxa®)	Boehringer Ingelheim GmbH	Investigational drug, not yet FDA approved
	Desirudin (Iprivask®)	Canyon Pharmaceuticals	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.
	Lepirudin (Refludan®)	Bayer Healthcare Pharmaceuticals	Anticoagulation in patients with heparin-associated thrombocytopenia and associated thromboembolic disease in order to prevent further thromboembolic complications.
Factor Xa Inhibitors	Rivaroxiban (Xarelto®)	Ortho-McNeil-Janssen	Investigational drug, not yet FDA approved
	Fondaparinux (Arixtra®)	GlaxoSmithKline	Prophylaxis of deep vein thrombosis in patients undergoing hip fracture surgery (including extended prophylaxis), hip replacement surgery, knee replacement surgery, or abdominal surgery; treatment of deep vein thrombosis or acute pulmonary embolism when administered in conjunction with warfarin

Table 2. Inferior Vena Cava Filters

Name	Manufacturer	FDA Approved Indication(s)
Stainless Steel Greenfield® Vena Cava Filter	Boston Scientific Corporation	Prevention of pulmonary embolism via placement in the vena cava in the following conditions: venous thrombosis or pulmonary thromboembolism when anticoagulants are contraindicated or inadequate for management of venous thrombosis with significant risk of, or following, pulmonary thromboembolism; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
Titanium Greenfield® Vena Cava Filter	Boston Scientific Corporation	Summary unavailable
Simon Nitinol Filter™ System	Bard Peripheral Vascular Inc	Preventing pulmonary embolism from migrating to the pulmonary arteries
Eclipse™ Vena Cava Filter	Bard Peripheral Vascular Inc	Prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy for thromboembolic disease; emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated
G2X® Filter System	Bard Peripheral Vascular Inc.	Prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

		pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy for thromboembolic disease; emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated
Recovery® G2® Filter System	Bard Peripheral Vascular Inc.	Prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy for thromboembolic disease; emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated
TRAPEASE® Permanent Vena Cava Filter	Cordis Corporation	Intended for the prevention of recurrent pulmonary embolism via percutaneous placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
OPTEASE® Retrievable Vena Cava Filter	Cordis Corporation	Intended for the prevention of recurrent pulmonary embolism via percutaneous placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
Vena Tech™ LP Vena Cava Filter	B. Braun Medical	Partial interruption of inferior vena cava to prevent pulmonary embolism as follows: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
Vena Tech™ LGM	B. Braun Medical	Partial interruption of inferior vena cava to prevent pulmonary embolism as follows: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
Gianturco-Roehm Bird's Nest® Vena Cava Filter	Cook Medical	Prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy in thromboembolic diseases;

		emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; prophylactically in patients with chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated
Cook Celect™ Vena Cava Filter	Cook Medical	Intended for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic
Gunther Tulip™ Vena Cava Filter	Cook Medical	Intended for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic
SafeFlo®	Rafael Medical Technologies	Intended for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated
Optional Vena Cava Filter	ALN Implants	Prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations: pulmonary thromboembolism when anticoagulants are contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; and chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated
Option Retrievable Vena Cava Filter	Rex Medical L.P	Intended for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following conditions: pulmonary thromboembolism when anticoagulant therapy is contraindicated; failure of anticoagulant therapy in thromboembolic diseases; emergency treatment following massive pulmonary embolism when anticipated benefits of conventional therapy are reduced; chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated

Table 3. Mechanical Devices

Name	Manufacturer	FDA Approved Indication(s)
Jobst® Anti-embolism Graduated	Jobst Institute Inc.	To prevent pooling of blood in legs

Compression Stocking	BSN Medical	
A-V Impulse System® Model 6060	Novamedix Services Limited	Acute and chronic edema, deep vein thrombosis prophylaxis, circulation enhancement, leg ulcers, leg pain incidental to leg trauma or surgery, venous stasis / venous insufficiency
Aircast® VenaFlow® System	DJO	Intended to apply intermittent application of pressure to a patient's calf, thigh or foot for the purpose of assisting blood flow in the veins.
SCD Express™ Compression System	Tyco Healthcare/Kendall	Circulation enhancement; deep vein thrombosis prophylaxis; acute and chronic edema; extremity pain incident to trauma or surgery; leg ulcers; venous stasis / venous insufficiency.

Outcomes

Final Health Outcomes

1. Fatal pulmonary embolism
2. Non-fatal pulmonary embolism
3. Major venous thromboembolism
4. Symptomatic venous thromboembolism
5. Total mortality
6. Mortality due to bleeding
7. Post thrombotic syndrome

Intermediate Health Outcomes

1. Deep vein thrombosis (asymptomatic or symptomatic, proximal or distal)

Harms, Adverse events

1. Bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion, surgical site bleeding)
2. Heparin induced thrombocytopenia
3. Discomfort
4. Re-operation
5. Re-admission
6. Insertion site thrombosis

Timing

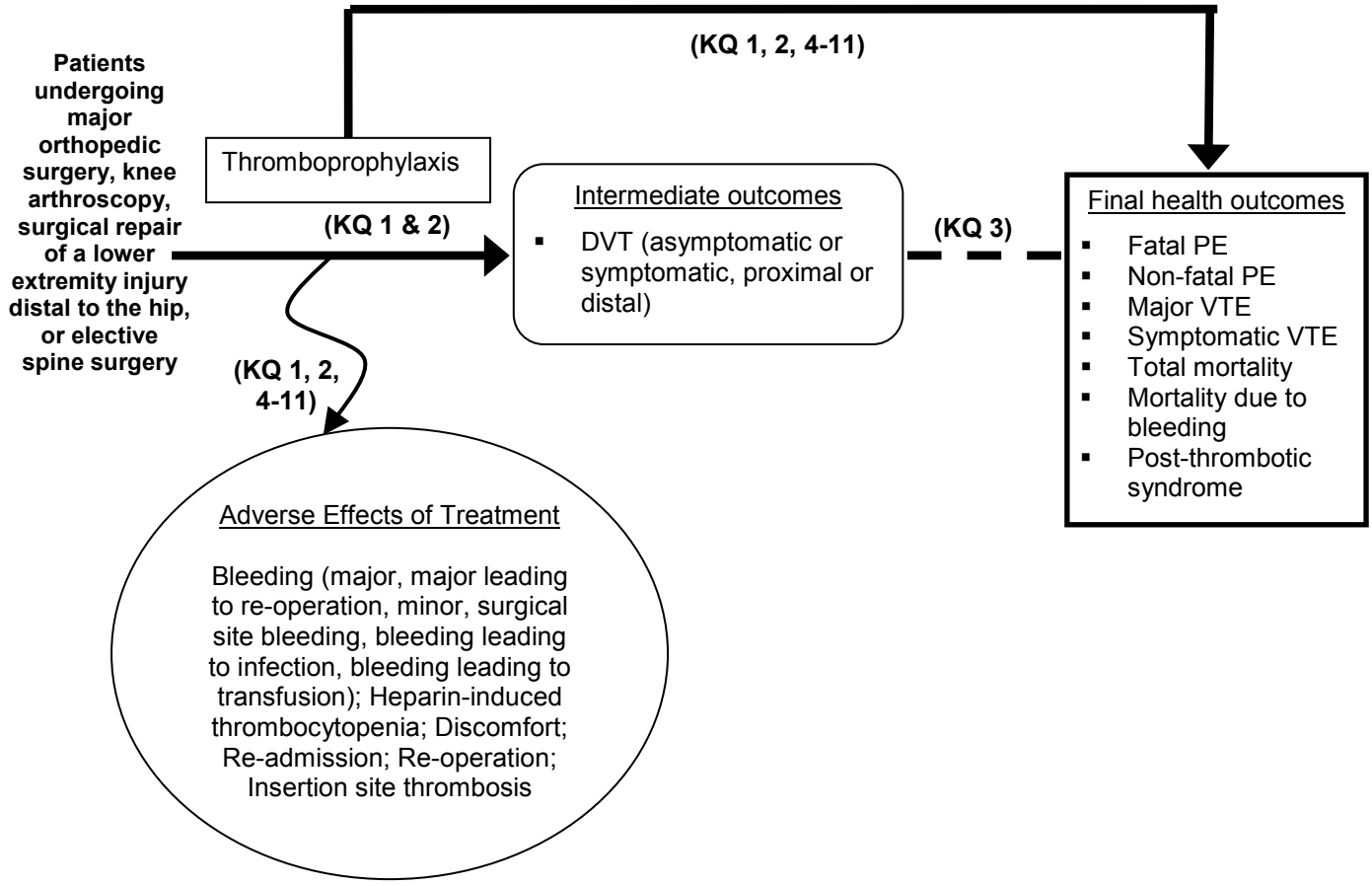
- Various durations of follow-up will be evaluated

Setting

- Inpatient orthopedic surgery

III. Analytic Framework

Figure 1. Provisional Analytic Framework for VTE Prophylaxis in Patients Undergoing Orthopedic Surgery



KQ: key question; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Two independent investigators will assess studies for inclusion in a parallel manner based on *a priori* defined criteria. In evaluating all KQs, RCTs of any size or controlled observational trials enrolling ≥ 750 patients will be included if they explicitly report the use of imagining studies to confirm VTE events (Doppler ultrasound or venography for DVT and spiral computed tomography (CT) angiography or ventilation/perfusion (V/Q) scan with either Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for PE). Observational studies will be limited to those with a larger sample size given that most contemporary RCTs in this topic area enroll over 1,000 patients. Therefore

observational studies would need to be of larger size to provide additional valuable information on outcomes of interest.

Additional inclusion criteria for the evaluation of KQ 1 are 1) inclusion of only patients undergoing major orthopedic surgery (TKR, THR, HFS) or report separate results for these major orthopedic surgeries; 2) studies which compare pharmacologic methods of thromboprophylaxis to placebo or to mechanical methods of prophylaxis or compare pharmacologic methods of thromboprophylaxis to each other in the absence of placebo controlled trials; and 3) report data on at least one pre-specified VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE; fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)] or bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion) outcome.

Additional inclusion criteria for the evaluation of KQ 2 are 1) inclusion of only patients undergoing major orthopedic surgery (TKR, THR, HFS) or report separate results for these major orthopedic surgeries; and 2) describe the association of patient or surgical/post-surgical characteristics and VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE; fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)] or bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion) outcomes.

Additional inclusion criteria for the evaluation of KQ 3 are 1) inclusion of only patients undergoing major orthopedic surgery (TKR, THR, HFS) or report separate results for these major orthopedic surgeries; 2) evaluate pharmacologic VTE prophylactic methods including dabigatran, rivaroxiban, or fondaparinux or report the predictors of pulmonary embolism; and 3) report data on both pulmonary embolism (asymptomatic or symptomatic) and deep vein thrombosis (asymptomatic or symptomatic). Trials evaluating dabigatran, rivaroxaban, and fondaparinux will be especially noteworthy as these trials are generally large (>1,000), report both symptomatic and asymptomatic VTE events, and are considered to reflect modern clinical practice.

Additional inclusion criteria in the evaluation of KQ 4-9 are 1) studies which compare pharmacologic or mechanical methods of thromboprophylaxis versus control or to each other, compare combination pharmacologic and mechanical methods of thromboprophylaxis to one or the other strategy, or compare use of an inferior vena cava filter to mechanical methods of thromboprophylaxis; and 2) report data on at least one pre-specified outcome including VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE; fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)]; post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion); heparin-induced thrombocytopenia; discomfort; re-admission; re-operation; total mortality; mortality due to bleeding; or insertion site thrombosis.

Additional inclusion criteria for the evaluation of KQs 10 and 11 are 1) include only patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or diskectomy all of the lumbar region) or report separate results for these orthopedic surgeries; 2) compare pharmacologic or mechanical methods of thromboprophylaxis versus control or compare injectable antithrombotic agents (LMWH, UFH, factor Xa antagonists, direct thrombin inhibitors) to mechanical interventions; and 3) report data on at least one pre-specified outcome including VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE; fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)]; post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion); heparin-induced thrombocytopenia; discomfort; re-admission; re-operation; total mortality; mortality due to bleeding.

Literature Search Strategies

Two independent investigators will conduct systematic literature searches of MEDLINE, the Cochrane Central Register of Controlled Trials, and SCOPUS from 1980 to the present. Language restrictions will not be imposed. Two separate searches of these databases will be conducted and the complete search strategies are included in Appendix A. The first search will be used to identify studies which evaluate pharmacologic, mechanical, or inferior vena cava filter methods of thromboprophylaxis in patients undergoing major orthopedic surgery, describe the association between patient or surgical/post-surgical characteristics and VTE or bleeding, or describe the association between intermediate and final health outcomes to answer KQs 1-9. The second search will be used to identify studies which evaluate pharmacologic or mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery to answer KQs 10 and 11. A manual search of references of clinical trials, meta-analysis, and systematic reviews will be conducted. A grey literature search will be conducted by the Scientific Resource Center and relevant citations will be added to our literature base.

The literature search will be updated concurrently with the peer review process. Newly identified literature will be evaluated using the aforementioned inclusion criteria by two independent reviewers. Relevant literature will be discussed with the Task Order Officer and it will be determined whether to incorporate it qualitatively or quantitatively into the report. This will all occur before the submission of the revised report.

Data Abstraction and Data Management

Two reviewers will use a standardized data abstraction tool to independently extract study data with disagreements resolved through discussion. The following data will be

collected from each trial if applicable: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population (inclusion and exclusion criteria, geographic location, thromboprophylaxis intervention, length of study, duration of patient follow-up), patient baseline characteristics and surgical /post-surgical characteristics (including characteristics which may modify risk of VTE or bleeding), thromboprophlyaxis regimen (name, strength, dose, frequency, route of administration and duration of therapy for pharmacologic interventions; name, frequency of use, and adherence for mechanical interventions, and name for IVC filters), mobilization status of the patients, use of concurrent standard medical therapies, data needed to assess intermediate and final health outcomes and adverse events, outcome definition, and diagnostic test used to confirm outcome of interest. Authors will be contacted for clarification or to provide additional data, if applicable.

Assessment of Methodological Quality of Individual Studies

Validity assessment will be performed using the recommendations in the EPC Methods Guide.[7] Each study will be assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals (percent follow-up), and potential conflict of interest. Additionally, randomized controlled trials will be assessed for randomization technique and allocation concealment. Observational studies will be assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies will then be given an overall score of good, fair, or poor (Table 4).

Table 4. Summary ratings of quality of individual studies

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

	serious errors in design, analysis, or reporting; large amounts of missing information, or discrepancies in reporting.

Data Synthesis

KQs 1 and 2 explore the baseline risk of VTE and bleeding and the patient and surgical/post-surgical characteristics that predict or differentiate the risk of VTE or bleeding in major orthopedic surgery. These questions will be answered by studies reflecting contemporary clinical practice (literature published in or after 1980). We will address KQ 1 qualitatively by reporting VTE and bleeding events rates. In the absence of placebo controlled trials, RCTs or large observational studies which compare pharmacologic VTE prophylaxis methods will be used to report VTE event rates. Baseline risk of bleeding will be summarized using event rates from trials or large observational studies including patients randomized to mechanical prophylaxis. We will address KQ 2 qualitatively by reporting predictors of VTE or bleeding identified in the literature.

KQ 3 explores the link between intermediate and final health outcomes. KQ 3 will be addressed by qualitatively reporting event rates of both asymptomatic and symptomatic pulmonary embolism and DVT from RCTs in patients undergoing major orthopedic surgery with use of the pharmacologic methods of VTE prophylaxis including dabigatran, rivaroxiban and fondaparinux. Results of large observational trials which report predictors of pulmonary embolism will be included for qualitative analysis.

The remaining KQs 4-11 explore the impact of thromboprophylaxis on final health outcomes and adverse effects. We will qualitatively examine data from all identified studies. For each outcome, we will conduct separate analyses of studies comparing each individual thromboprophylactic intervention with control and studies in which different thromboprophylactic interventions were compared to each other. KQs 5-9 and 11 explore direct comparisons between or within specified classes and therefore only direct comparison trials will be used in analyzing these KQs quantitatively. When answering KQs 10 and 11, elective spine surgery will be analyzed separately from knee arthroscopy and lower extremity injuries distal to the hip requiring surgical repair.

We will conduct meta-analyses when 2 or more studies adequate for pooling are available for any outcome. Randomized controlled trials (RCTs) will be pooled separately from observational studies with a control group. For dichotomous outcomes, weighted averages will be reported as relative risks (RRs) and risk differences (RDs) with associated 95 percent confidence intervals (CIs). As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model will be used when pooling data and calculating RRs, RDs and 95 percent CIs.[8] When pooling continuous endpoints, a weighted mean difference (WMD) will be calculated using a DerSimonian and Laird random effects model.[9] In cases where mean change scores from baseline for each group are not reported, we will calculate the difference between the mean baseline and mean follow-up scores for each group. Standard deviations (SDs) of the change scores will be calculated using the method proposed by Follman and colleagues.[10] In the event that there is more than one method of throboprophylaxis being compared with another method of thromboprophylaxis (i.e. low-molecular weight heparin versus low-molecular weight heparin plus compression stockings versus compression stockings), each method of thromboprophylaxis will be compared

individually against the other (as a separate trial) by dividing the control group equally between the comparisons.[8]

Statistical heterogeneity will be addressed using the I^2 statistic (which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity). While categorization of values for I^2 may not be appropriate in all situations, I^2 values of 25 percent, 50 percent and 75 percent have been regarded as representative of low, medium and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger's weighted regression statistics will be used to assess for the presence of publication bias. Statistics will be performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 will be considered statistically significant for all analyses.

Subgroup and sensitivity analyses will be conducted to assess the effect of heterogeneity (both clinical and methodological) on our meta-analysis' conclusions. KQs 1-9 evaluate patient's undergoing major orthopedic surgery; we will evaluate the results separately based on the type of surgery: total knee replacement, total hip replacement, and hip fracture surgery. KQs 10 and 11 evaluate patients undergoing other orthopedic surgeries; we will evaluate the results separately based on the type of surgery. For each KQ, we will also evaluate the results based on the year of publication (earlier than 2001 vs. 2001 to present), gender, ethnicity, and patient age. For KQs 4-11 components of the pharmacologic thromboprophylactic regimen (i.e. dose, INR goal), mechanical thromboprophylactic regimen (i.e. compliance with device, duration of wear), method of confirming events (i.e. studies which adjudicate events vs. those that do not) and definitions used to define final health outcomes (i.e. VTE) and adverse events (i.e. bleeding) in the trials will be considered for subgroup and sensitivity analysis when data is available.

Grading the Strength of Evidence

We will use EPC GRADE (Grading of Recommendations Assessment, Development) to assess the strength of evidence. This system uses four required domains – risk of bias, consistency, directness, and precision.[11] Additional domains will be utilized when they are determined to be relevant to this review. All assessments will be made by two investigators (with disagreements resolved through discussion). The evidence pertaining to each KQ will be classified into three broad categories: (1) "high", (2) "moderate", or (3) "low" grade (Table 5). Below we describe in more detail the features that determined the strength of evidence for the different outcomes evaluated in this report.

Table 5. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further

	research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Risk of bias

Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. For study design, whether the study was a randomized controlled trial or an observational study will be recorded. Studies will be ranked as having no limitations, serious limitations, or very serious limitations.

Consistency

Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We will assess whether or not the effect sizes were on the same side of unity; whether the range of effect sizes was narrow, and the degree of statistical heterogeneity in evaluating consistency. We will rank this domain as no inconsistency, serious inconsistency, and very serious inconsistency. When only a single study is included, consistency can not be judged.

Directness

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We will rank this domain as no indirectness, serious indirectness, and very serious indirectness.

Precision

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we will evaluate the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

Rating Applicability of Evidence

Effectiveness studies will meet five of the following seven criteria: primary care population, less stringent eligibility criteria, assessed final health outcomes, adequate study duration with clinically relevant treatment modalities, assessed adverse events,

had an adequate sample size, and used intention to treat analysis.[12] Studies meeting less than 5 criteria would be classified as efficacy trials and be deemed to have less applicability. In addition, factors identified in Table 6 are important when determining applicability and will be extracted into evidence tables for every study. Given these inputs, the applicability of each study will be determined. Using all of the studies to answer a KQ, the applicability of the body of evidence will be determined and reported qualitatively.

Table 6. Applicability PICOTS and data to extract

Feature	Condition that limits applicability	Features to be extracted into evidence table
Population	Differences between patients in study and the community	Eligibility criteria, demographics
Population	Events rates markedly different than in community	Event rates in treatment and control groups
Intervention	Treatment not reflective of current practice	Complete regimen of thromboprophylactic intervention (pharmacologic, mechanical, or IVC filter)
Comparator	Use of substandard alternative therapy	Type of comparator
Outcomes	Surrogate endpoints, brief follow-up periods, improper definitions for outcomes, composite endpoints	Outcomes (benefits and harms) and how they were defined and diagnosed
Settings	Settings where standards of care differ markedly from setting of interest	Clinical Setting and geographic setting

V. References

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11. Schunermann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendation. The GRADE Working Group; 2008.
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Source: ***www.effectivehealthcare.ahrq.gov***
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VI. Definition of Terms

Term	Definition
AAOS	American Academy of Orthopedic Surgeons
ACCP	American College of Chest Physicians
ASA	Aspirin
CI	Confidence interval
CT	Computed tomography
DVT	Deep vein thrombosis
EPC	Evidence based practice center
GCS	Graduated compression stocking
GRADE	Grading of Recommendations Assessment Development
HFS	Hip fracture surgery
IPC	Intermittent pneumatic compression
IVC	Inferior vena cava filter
KQ	Key question
LDUH	Low density unfractionated heparin
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
RCT	Randomized controlled trial
RR	Relative risk
THR	Total hip replacement
TKR	Total knee replacement
V/Q	Ventilation/perfusion
VFP	Venous foot pump
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WMD	Weighted mean difference

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

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Appendix A: Search Strategies

Search 1: Major orthopedic surgery

MEDLINE and Cochrane Central Register of Controlled Trials (OVID)

1. arthroplasty, replacement, knee/
2. knee.mp AND arthroplasty/
3. total knee replacement.mp
4. knee arthroplasty.mp
5. TKR.mp
6. knee prosthesis/
7. knee prosthesis.mp
8. knee joint.mp
9. arthroplasty, replacement, hip/
10. hip.mp AND arthroplasty/
11. total hip replacement.mp
12. hip arthroplasty.mp
13. THR.mp
14. hip prosthesis/
15. hip prosthesis.mp
16. hip fracture surgery.mp
17. HFS.mp
18. hip.mp AND fracture fixation, internal/
19. or/1-18
20. pulmonary embolism/
21. pulmonary embol*.mp
22. pulmonary thromboembol*.mp
23. PE.mp
24. deep vein thrombos*.mp
25. deep venous thrombos*.mp
26. deep venous thromboembol*.mp
27. deep vein thromboembol*.mp
28. DVT.mp
29. venous thromboembolism/
30. venous thromboembol*.mp
31. VTE.mp
32. venous thrombosis/
33. venous thrombos*.mp
34. clot.mp
35. or/20-34
36. anticoagulants/
37. aspirin/
38. aspirin.mp
39. clopidogrel.mp
40. ticlopidine.mp
41. prasugrel.mp

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42. heparin/
43. heparinoids/
44. heparin.mp
45. UFH.mp
46. heparin, low-molecular weight/
47. low molecular weight heparin.mp
48. LMWH.mp
49. enoxaparin.mp
50. dalteparin.mp
51. nadroparin.mp
52. ardeparin.mp
53. bemiparin.mp
54. certoparin.mp
55. parnaparin.mp
56. reviparin.mp
57. tinzaparin.mp
58. danaparoid.mp
59. fondaparinux.mp
60. idraparinux.mp
61. rivaroxaban.mp
62. hirudins/
63. desirudin.mp
64. argatroban.mp
65. bivalirudin.mp
66. lepirudin.mp
67. dabigatran.mp
68. warfarin/
69. 4-Hydroxycoumarins/
70. warfarin.mp
71. acenocoumarol.mp
72. dicoumarol.mp
73. dextran sulfate/
74. dextran sulfate.mp
75. or/36-74
76. stockings, compression/
77. compression stocking.mp
78. compression stockings.mp
79. compression boot.mp
80. graduated compression stocking.mp
81. graduated compression stockings.mp
82. elastic stocking.mp
83. elastic stockings.mp
84. graduated compression stocking.mp
85. graduated compression stockings.mp
86. GCS.mp
87. venous foot pump.mp

Source: ***www.effectivehealthcare.ahrq.gov***
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88. VFP.mp
89. intermittent pneumatic compression devices/
90. intermittent pneumatic compression.mp
91. pneumatic compression stocking.mp
92. pneumatic compression stockings.mp
93. pneumatic hose.mp
94. pneumatic compression hose.mp
95. IPC.mp
96. or/76-95
97. vena cava filters/
98. vena cava filter.mp
99. vena cava filters.mp
100. IVC.mp
101. or/97-100
102. 75 or 96 or 101
103. 19 and 35 and 102

SCOPUS

((((ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin OR parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin OR lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (((((ALL(compression stocking$)) OR (ALL(graduated compression stocking$)) OR (ALL(elastic stocking$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)))) OR (ALL(pneumatic compression)))))) AND (((((ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)) OR (ALL(venous thromboembol*)) OR (ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)))) OR (((ALL(venous thromboembol*)) OR (ALL(pulmonary thromboembol*)) OR (ALL(pulmonary embol*)) OR (ALL(venous thrombos*)))))) AND (((ALL(knee replacement)) OR (ALL(knee arthroplasty)) OR (ALL(hip arthroplasty)) OR (ALL(hip replacement)) OR (ALL(hip fracture surgery)))))

Search 2: Other orthopedic surgery

MEDLINE and Cochrane Central Register of Controlled Trials (OVID)

1. knee arthroscop*
2. arthroscop* adj knee
3. meniscectomy ADJ arthroscop*
4. synovectomy ADJ arthroscop*
5. cruciate ligament AND (arthroscop* OR repair)
6. casts, surgical/ OR casts, surgical.mp
7. plaster cast.mp

8. splint*.mp OR splints/
9. Achilles ADJ tendon
10. tibial plateau fracture.mp
11. distal ADJ femur fracture.mp
12. lumbar ADJ laminectomy.mp
13. lumbar ADJ diskectomy.mp
14. lumbar ADJ spinal fusion.mp
15. (fracture fixation, internal/ OR fracture fixation, intramedullary/) AND (femur OR femor* OR tibia* OR ankle OR foot)
16. osteotomy.mp AND (femur OR femor* OR tibia*)
17. or/1-16
18. anticoagulants/
19. aspirin/
20. aspirin.mp
21. clopidogrel.mp
22. ticlopidine.mp
23. prasugrel.mp
24. heparin/
25. heparinoids/
26. heparin.mp
27. UFH.mp
28. heparin, low-molecular weight/
29. low molecular weight heparin.mp
30. LMWH.mp
31. enoxaparin.mp
32. dalteparin.mp
33. nadroparin.mp
34. ardeparin.mp
35. bemiparin.mp
36. certoparin.mp
37. parnaparin.mp
38. reviparin.mp
39. tinzaparin.mp
40. danaparoid.mp
41. fondaparinux.mp
42. idraparinux.mp
43. rivaroxaban.mp
44. hirudins/
45. desirudin.mp
46. argatroban.mp
47. bivalirudin.mp
48. lepirudin.mp
49. dabigatran.mp
50. warfarin/
51. 4-Hydroxycoumarins/
52. warfarin.mp

53. acenocoumarol.mp
54. dicoumarol.mp
55. dextran sulfate/
56. dextran sulfate.mp
57. or/18-56
58. stockings, compression/
59. compression stocking.mp
60. compression stockings.mp
61. compression boot.mp
62. graduated compression stocking.mp
63. graduated compression stockings.mp
64. elastic stocking.mp
65. elastic stockings.mp
66. graduated compression stocking.mp
67. graduated compression stockings.mp
68. GCS.mp
69. venous foot pump.mp
70. VFP.mp
71. intermittent pneumatic compression devices/
72. intermittent pneumatic compression.mp
73. pneumatic compression stocking.mp
74. pneumatic compression stockings.mp
75. pneumatic hose.mp
76. pneumatic compression hose.mp
77. IPC.mp
78. or/58-77
79. pulmonary embolism/
80. pulmonary embol*.mp
81. pulmonary thromboembol*.mp
82. PE.mp
83. deep vein thrombos*.mp
84. deep venous thrombos*.mp
85. deep venous thromboembol*.mp
86. deep vein thromboembol*.mp
87. DVT
88. venous thromboembolism/
89. venous thromboembol*.mp
90. VTE
91. venous thrombosis/
92. venous thrombos*.mp
93. clot.mp
94. or/79-93
95. 57 or 78
96. 17 and 94 and 95

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((((((lumbar PRE/1 spinal fusion) OR (lumbar PRE/1 diskectomy) OR (lumbar PRE/1 laminectomy) OR (open reduction internal fixation PRE/1 ankle) OR (open reduction internal fixation PRE/1 foot))) OR (((open reduction internal fixation PRE/1 tibia*) OR (open reduction internal fixation PRE/1 femur*) OR (osteotomy PRE/1 femur*) OR (osteotomy PRE/1 tibia*) OR (distal PRE/1 femur* fracture) OR (tibial plateau fracture) OR (intermedullary fixation))))) AND (((((ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)) OR (ALL(venous thromboembol*)) OR (ALL(deep vein thrombos*)) OR (ALL(deep venous thrombos*)))) OR (((ALL(venous thromboembol*)) OR (ALL(pulmonary thromboembol*)) OR (ALL(pulmonary embol*)) OR (ALL(venous thrombos*)))))