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Comparative Effectiveness Review

Number xx

Venous thromboembolism prophylaxis in orthopedic surgery

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Preface

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

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

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

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

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

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

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

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Structured Abstract

Objectives: This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) examining the comparative efficacy and safety of prophylactic strategies in orthopedic surgery.

Data Sources: Medline, the Cochrane Central Register of Controlled Trials, and Scopus from 1980 to September 2010 with no language restrictions.

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

Results: In major orthopedic surgery [total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery (HFS), respectively], the incidence of DVT (39 percent, 53 percent, 47 percent), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), and minor bleeding (6 percent, 5 percent, --) were reported in the placebo/control groups of clinical trials. The SOE and AOE was predominantly low for THR and TKR but the SOE for HFS was insufficient. In major orthopedic surgery, pharmacologic prophylaxis reduced major venous thromboembolism (VTE) [OR 0.21 (0.05-0.95), NNT 19-22, SOE: L, AOE: L], DVT [RR 0.55 (0.45-0.67), NNT 3-11, SOE: M, AOE: L], and proximal DVT (pDVT) [RR 0.53 (0.39-0.73,), NNT 6-79, SOE: M, AOE: L] but increased minor bleeding [RR 1.61 (1.12-2.32), NNH 4-166, SOE: H, AOE: M]. Prolonged prophylaxis for ≥28 days was superior to prophylaxis for 7 to 10 at reducing symptomatic objectively confirmed VTE [RR 0.38 (0.19-0.77), NNT 8-54, SOE: M, AOE: L], PE [OR 0.13 (0.04-0.47), NNT 24-232, SOE: H, AOE: L], DVT [RR 0.37 (0.21-0.64), NNT 5-22, SOE: M, AOE: M], and pDVT [RR 0.29 (0.16-0.52), NNT 9-71, SOE: H, AOE: M] but increased minor bleeding [OR 2.44 (1.41-4.20), NNH 11-118, SOE: H, AOE: M]. Using both pharmacologic and mechanical prophylaxis reduced DVT [RR 0.48 (0.32-0.72), NNT 3-67, SOE: M, AOE: M] versus pharmacologic prophylaxis alone.

Low molecular weight heparins (LMWHs) reduced PE [OR 0.48 (0.24-0.95), NNT 8, SOE: M, AOE: L], DVT [RR 0.80 (0.65-0.99), NNT 12-100, SOE: M, AOE: L], pDVT [RR 0.60 (0.38-0.93), NNT 14-50, SOE: H, AOE: L], major bleeding [OR 0.57 (0.37-0.88, NNT 41, SOE: H, AOE: L], and heparin induced thrombocytopenia [OR 0.12 (0.03-0.43), NNT 34-202, SOE: M, AOE: L] versus unfractionated heparin. LMWHs reduced DVT [RR 0.66 (0.55-0.79), NNT 6-13, SOE: L, AOE: M] but increased major bleeding [RR 1.92 (1.27-2.91), NNH 57-220, SOE: H, AOE: M], minor bleeding [RR 1.23 (1.06-1.43), NNH 18-218, SOE: M, AOE: M], and

surgical site bleeding [OR 2.63 (1.31-5.28), NNH 23-64, SOE: L, AOE: L] versus vitamin K antagonists. LMWHs increased DVT [RR 2.06 (1.66-2.55), NNH 8-24, SOE: L, AOE: M] and pDVT [OR 2.24 (1.55-3.24), NNH 43-83, SOE: M, AOE: L] but reduced major bleeding [OR 0.65 (0.48-0.89), NNT 74-145, SOE: H, AOE: L] versus factor Xa inhibitors. Antiplatelets increased DVT [1.63 (1.11-2.39), NNH 4-27, SOE: M, AOE: L] versus mechanical prophylaxis. Unfractionated heparin increased DVT [RR 2.31 (1.34-4.00), NNH 5-11, SOE: M, AOE: L] and pDVT [OR 4.74 (2.99-7.49), NNH 11, SOE: M, AOE: L] versus direct thrombin inhibitors. Intermittent compression stocking decreased DVT [RR 0.06 (0.01-0.41), NNT 3-67, SOE: L, AOE: L] versus graduated compression stockings.

We did not have adequate information to evaluate the role of inferior vena cava filter (IVC) filters or to evaluate the impact of prophylaxis on orthopedic surgeries aside from THR, TKR, and HFS.

Conclusions: In major orthopedic surgery, the incidence of DVT is appreciable but the risk of PE, major and minor bleeding is smaller. The balance of benefits to harms is favourable for providing prophylaxis to these patients and to extend the period of prophylaxis beyond the standard 7-10 days. The comparative balance of benefits to harms for LMWHs are superior to unfractionated heparin. Other interclass comparisons either could not be made due to lack of data, showed similarities between classes on outcomes, or had offsetting effects where benefits of one class on efficacy was tempered by an increased risk of bleeding. The balance of benefits to harms for dual pharmacologic plus mechanical prophylaxis versus either strategy alone could not be determined. We could not determine the impact of IVC filters on outcomes or the impact of prophylaxis on other orthopedic surgeries.

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Effective Health Care

Venous Thromboembolism Prophylaxis in Orthopedic Surgery

Executive Summary

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Background

Major orthopedic surgery (total hip replacement [THR], total knee replacement [TKR] or hip fracture surgery [HFS]) carries a risk of venous thromboembolism (VTE) and its components of pulmonary embolism (PE) and deep venous thrombosis (DVT). A variety of strategies to prevent VTE are available including pharmacological (antiplatelet, anticoagulant) and mechanical modalities which can be used alone or in combination.[1] In contemporary practice, the risk of VTE, PE, and DVT and the causal link between DVT and PE has not been well established. [2] In addition to major orthopedic surgery, there are a variety of other orthopedic surgeries and the impact of prophylaxis has not been well evaluated.

While prophylactic strategies may decrease the risk of VTE, DVT, and PE, the magnitude of benefit in contemporary practice using rigorous definitions of endpoints when limited to the available medications or devices available within the United States is not well known. The impact of duration of prophylaxis on outcomes, whether dual prophylactic therapy is superior to single modality therapy, and the comparative effectiveness of different modalities has not been adequately systematically reviewed. To determine comparative effectiveness, both the benefits and harms of competing prophylactic treatments need to be appreciated.

Objectives

To perform a comparative effectiveness review examining the benefits and harms associated with VTE prophylaxis in patients undergoing major orthopedic surgery, other orthopedic surgery or arthroscopy. We sought to answer the following 11 key questions (KQ):

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

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

KQ 3: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of 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?

KQ 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 (LMWHs), injectable unfractionated heparin (UFH), injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors (DTIs), oral vitamin K antagonists (VKAs)] or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump)] compared to no thromboprophylaxis on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, post thrombotic syndrome (PTS), mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia (HIT), discomfort, readmission, and reoperation?

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

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

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

bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

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

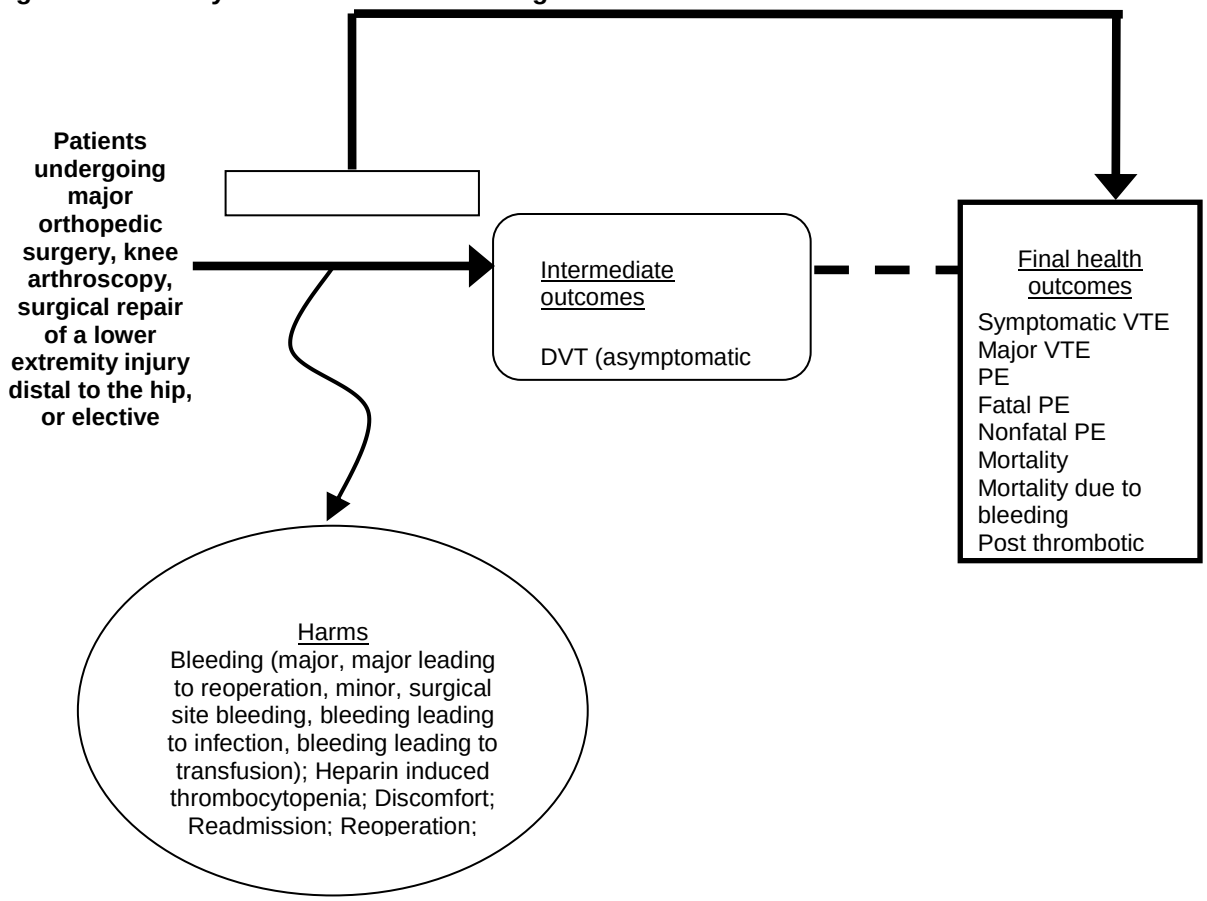
KQ 9: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter (IVC) placement compared to any external mechanical intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, reoperation and IVC filter placement associated insertion site thrombosis?

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

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

Analytic Framework

Figure ES 1. Analytic framework connecting intermediate to final health outcomes.



Methods

Input from Stakeholders

The EPC drafted a topic refinement document with proposed key questions after consult with Key Informants. Our Key Informants did not have financial or other declared conflicts. The public was invited to comment on the topic refinement document and key questions. After reviewing the public commentary, responses to public commentary, proposed revisions to the key questions, and a preliminary protocol was generated and reviewed with the Technical Expert Panel. Our Technical Expert Panel provided feedback on the feasibility and importance of our approach and provided their unique insight. Again, no conflict of interest was identified. The draft CER report will undergo peer review and public commentary and revisions will be made before being finalized.

Data Sources and Selection

Two independent investigators conducted systematic literature searches of Medline, the Cochrane Central Register of Controlled Trials, and Scopus from 1980 to September 2010 with

no language restrictions. Two separate literature searches were conducted. The first search was 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, surgical, or postsurgical characteristics and VTE or bleeding, or describe the association between intermediate and final health outcomes to answer KQs 1 through 9. The second search was used to identify studies which evaluate pharmacologic or mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery to answer KQs 10 and 11. Backward citation tracking and a grey literature search were also conducted, with relevant citations added to our literature base.

Two independent investigators assessed 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 were included if they explicitly reported 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).

For KQ 1 and KQ 2, only studies of patients undergoing major orthopedic surgery (TKR, THR, HFS) that included an outcome of interest were included. For efficacy outcomes in KQ 1, only placebo or control arms of studies were eligible, while for bleeding these arms or mechanical prophylaxis arms were eligible. For KQ 2, studies needed to describe the association of patient, surgical or postsurgical characteristics with an outcome and made adjustments for confounding (multivariable logistic regression, randomization, or propensity score matching/adjustment. For KQ 3, only studies of patients undergoing major orthopedic surgery (TKR, THR, HFS) were included if they evaluated pharmacologic VTE prophylactic methods or reported the predictors of PE and reported data on both PE (asymptomatic or symptomatic) and DVT (asymptomatic or symptomatic).

For KQ 4 through 9 studies had to 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 report data on at least one prespecified outcome. Studies included in KQ 10 and KQ 11 needed to report on a prespecified outcome and compare pharmacologic or mechanical methods of thromboprophylaxis but 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 with or without decompression, laminectomy, or diskectomy all of the lumbar region)

Data Extraction and Quality Assessment

Two reviewers used a standardized data extraction tool to independently extract study data with disagreements resolved through discussion. The following data was collected: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, patient baseline, surgical and postsurgical characteristics, thromboprophlyaxis regimen, mobilization status of the patients, use of concurrent standard

medical therapies, data needed to assess intermediate and final health outcomes and adverse events.

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

For applicability assessment, effectiveness studies met five of the following seven criteria: 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. Studies meeting less than five criteria would be classified as efficacy trials and deemed to have less applicability. Specific patient, intervention, comparator, outcome, and setting factors that limit applicability were also evaluated and extracted to derive a determination of individual study applicability.

Data Synthesis and Analysis

We conducted meta-analyses when two or more RCTs adequate for pooling were available for any outcome. Data from observational studies were not pooled. For dichotomous outcomes, weighted averages were reported as proportions (KQ 1 only), Peto's odds ratios (OR) or relative risks (RRs) with associated 95 percent confidence intervals (CIs). As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model was used, (except for Peto's OR). Statistical heterogeneity was addressed using the I^2 statistic. Egger's weighted regression statistics was used to assess for publication bias. Statistics were performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England).

We used EPC GRADE (Grading of Recommendations Assessment, Development) to assess the strength of evidence. This system uses four required domains (risk of bias, consistency, directness, and precision) and classifies into four broad categories: "high", "moderate", "low", or insufficient grade. The applicability of evidence was rated into the same categories qualitatively based on the conglomeration of the individual studies applicability.

Results

Results of search one and two are given in Figure ES 2 and Figure ES 3.

Of the 173 articles included in search one, 120 articles represented 97 unique randomized controlled trials (N=44,214)[3-12,12-119] and 14 articles represented 13 unique controlled observational studies (N=480,241).[120-133] Thirty-nine citations represented 39 systematic reviews/meta-analyses.[134-172].

The second literature search yielded two unique randomized controlled trials (N=235)[173,174] and four articles representing three unique meta-analyses.[175-178]

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

Key Question 1: Data was limited to placebo or control arms of trials for PE and DVT outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native incidence of DVT events was still relatively high but PE and bleeding events were rarer. In THR, TKR, and HFS, respectively, the incidences reported in clinical trials were: DVT (39 percent, 53 percent, 47 percent), proximal DVT (32 percent, 17 percent, --), distal DVT (30 percent, 30 percent, --), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (6 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --). There was high heterogeneity which could reflect different time periods of followup, different definitions of events, and different ethnicities and countries in trials.

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

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

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

scheduled anticoagulant treatment for DVT once it was detected may have diminished the percentage that developed into PE.

Key Question 4: Providing pharmacologic prophylaxis versus no prophylaxis has a better comparative balance of benefits to harms. There is moderate evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases DVT (overall, proximal, and distal) in patients undergoing major orthopedic surgery. There is low evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major VTE and asymptomatic DVT in patients undergoing major orthopedic surgery. Pharmacologic prophylaxis did not significantly impact PE in the base case analysis, although it was trending in that direction, and significantly reduced the risk of PE in the most stringent trials where they did not allow any background prophylaxis (such as compressions stockings) in the experimental groups. There is moderate evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis does not significantly impact nonfatal PE, mortality, symptomatic DVT or major bleeding in patients undergoing major orthopedic surgery. We could not determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group.

Providing mechanical prophylaxis versus no prophylaxis may have a better comparative balance of benefits to harms but more data is needed to support this assumption. There was a low level of evidence that mechanical prophylaxis versus no prophylaxis significantly decreased the occurrence of DVT in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal DVT in patients undergoing major orthopedic surgery, the power to detect these differences was low. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use so benefits would likely overwhelm the risk of harms.

Key Question 5: While we sought to determine the impact of therapy on numerous outcomes, we were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, there was either a lack of evaluable data or no significant differences were found. We could not determine if this means that there is a lack of effect versus a lack of power to show that it is significant.

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

LMWH agents were compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving LMWHs.

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

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

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

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

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

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

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

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

Key Question 7: The balance of benefits to harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic

surgery could not be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis did not significantly impact nonfatal PE, mortality, or DVT subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There was moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of DVT versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes could not be determined.

Key Question 8: Prolong prophylaxis had a better comparative balance of benefits to harms versus short term prophylaxis in patients undergoing major orthopedic surgery. The impact of prolonging prophylaxis for 28 days or longer on events was compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. In base case analyses, prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed VTE, PE (overall and nonfatal), and DVT (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. While higher heterogeneity was found for symptomatic VTE and DVT, the direction of effect was consistent between all of the trials. In base case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis.

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

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

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

Figure ES 2. PRISMA flow diagram for search one

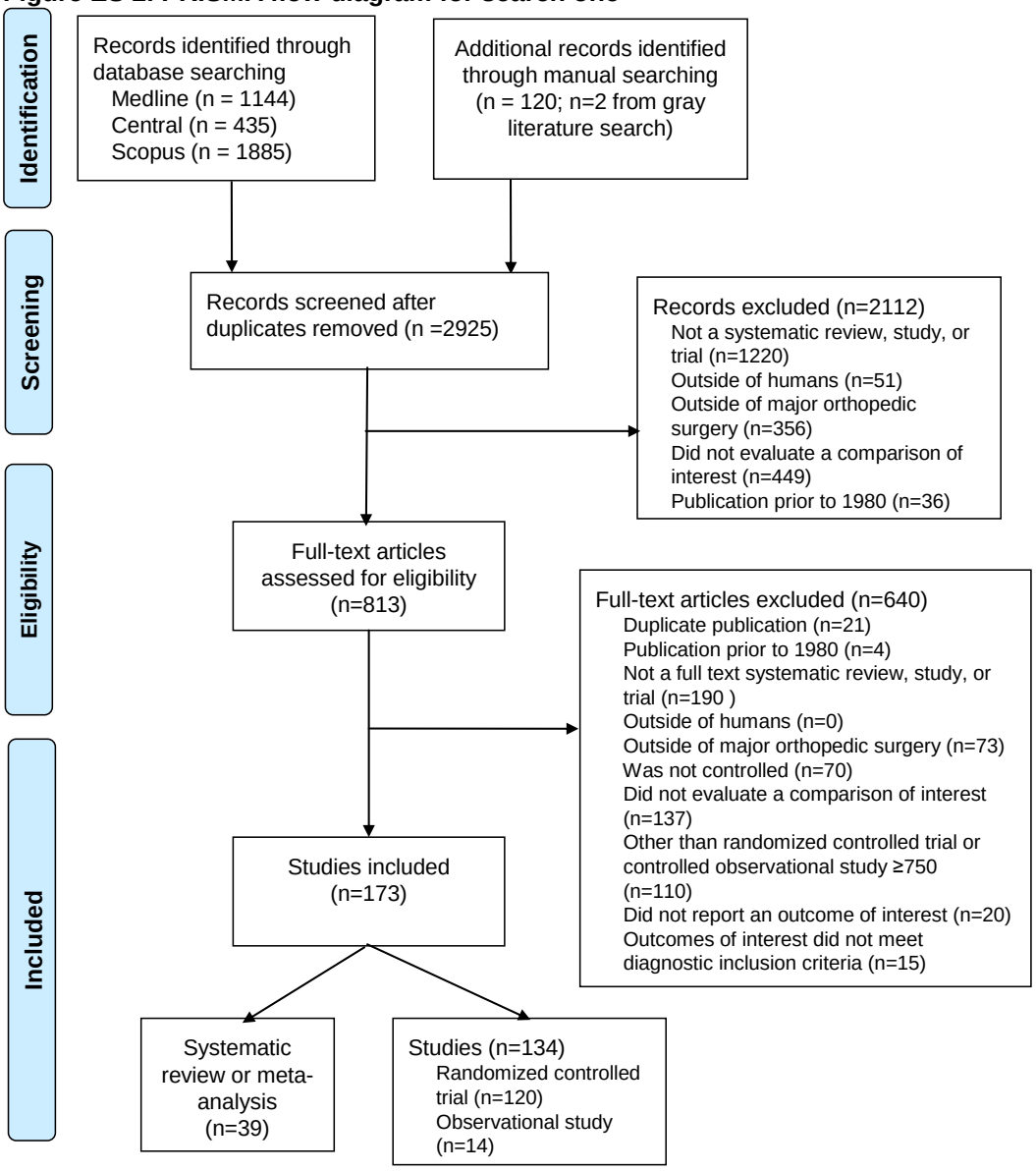


Figure ES 3. PRISMA flow diagram for search two

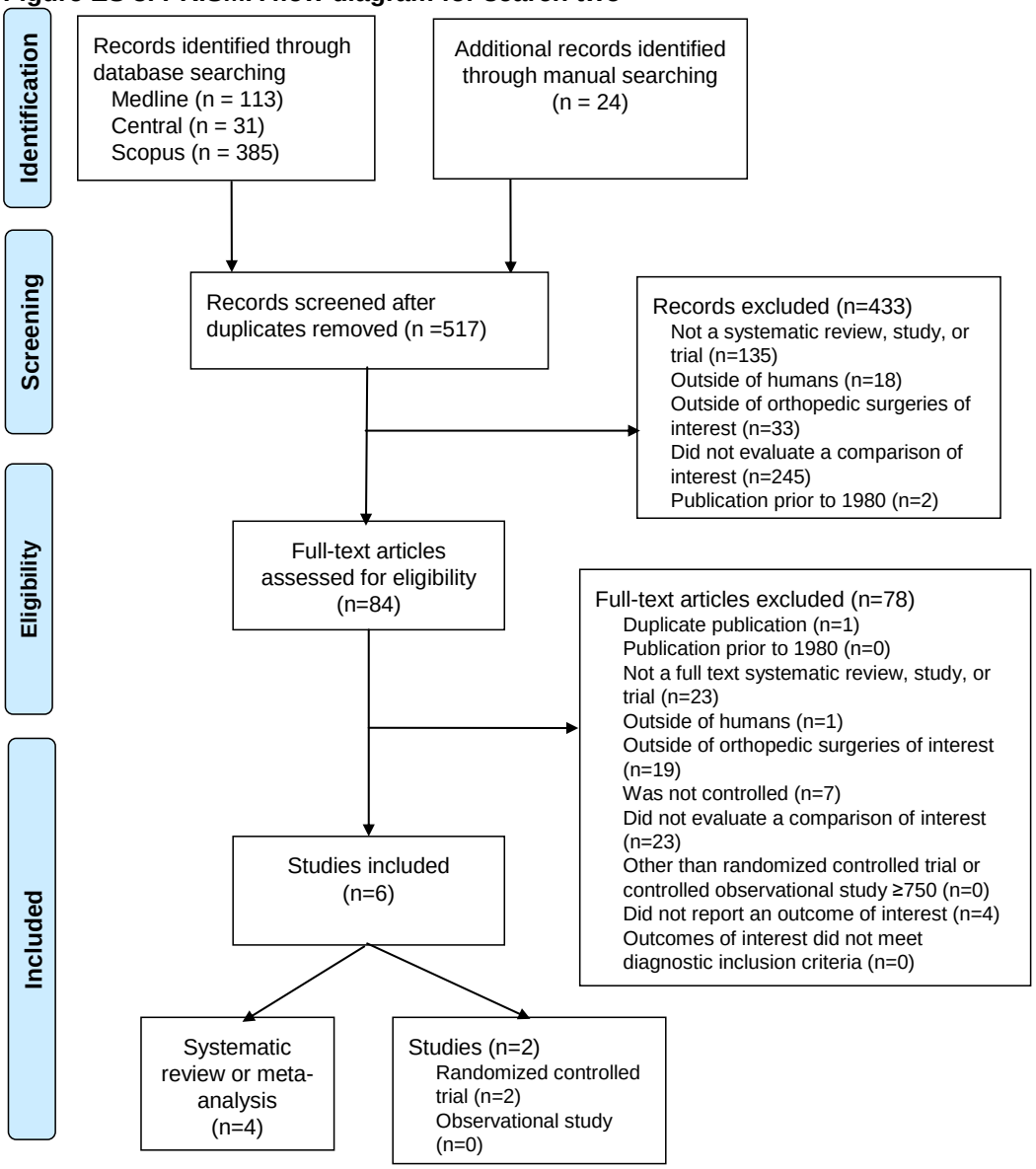


Table ES-1. Summary of results from base case analyses in patients who had major orthopedic surgery* [3-133]

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 1. Incidence of health outcomes in total hip replacement					
PE	5 RCT	Yes	Pooled incidence of 6% (0.3% to 18%)	L	L
DVT	8 RCT	Yes	Pooled incidence of 39% (25% to 53%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 24%		
Proximal DVT	4 RCT	Yes	Pooled incidence of 32% (14% to 54%)	L	L
	1RCT	No	One trial not suitable for pooling had an incidence of 14%		
Distal DVT	2 RCT	Yes	Pooled incidence of 30% (4% to 68%)	L	L
	1 RCT	No	One trial not suitable for pooling had in incidence of 17.3%		
Major bleeding	5 RCT	Yes	Pooled incidence of 1% (0.2% to 3%)	M	L
Minor bleeding	5 RCT	Yes	Pooled incidence of 6% (1% to 16%)	L	M
KQ 1. Incidence of health outcomes in total knee replacement					
PE	2 RCT	Yes	Pooled incidence of 1% (0.07% to 4%)	L	L
	1 OBS	No	The observational study had an incidence of 0.3%		
DVT	2 RCT	Yes	Pooled incidence of 46% (5% to 91%)	L	L
	1 RCT, 1 OBS	No	One trial not suitable for pooling had an incidence of 68.8% and the observational study had an incidence of 0%		
Proximal DVT	2 RCT	Yes	Pooled incidence of 17% (1% to 66%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 18.8%		
Distal DVT	2 RCT	Yes	Pooled incidence of 22% (12% to 35%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 40.6%		
Major bleeding	2 RCT	Yes	Pooled incidence of 3% (0.2% to 8%)	L	L
Minor bleeding	2 RCT	Yes	Pooled incidence of 5% (3% to 8%)	M	L
KQ 2. Impact of surgical characteristics on outcomes					
General versus regional anesthesia					
DVT	4 RCT, 2 OBS	No	The majority of trials showed that regional anesthesia was associated with a decrease in the risk of DVT while observational data was conflicting.	L	L
Symptomatic DVT	2 RCT	No	No significant difference	L	L
Proximal DVT	5 RCT	No	No significant difference	L	L
Cemented versus non cemented arthroplasty					
DVT	2 RCT, 3 OBS	No	No significant difference	L	L
pDVT	2 RCT	No	No significant difference	L	L
KQ 2. Impact of patient characteristics on outcomes					
Congestive heart failure					
Symptomatic objectively confirmed VTE	2 OBS	No	Significantly increases odds	M	M
Age					

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
Symptomatic objectively confirmed VTE	2 OBS	No	No significant impact	L	M
DVT	3 OBS	No	Significantly increased risk	L	L
KQ 4-8. Symptomatic objectively confirmed VTE					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.71 (0.49 to 1.04)	L	M
LMWH versus VKA	2 RCTs	Yes	No significant difference, OR 1.00 (0.69 to 1.46)	L	M
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.38 (0.19 to 0.77), NNT 8 to 54	M	L
KQ 4-8. Major VTE					
Pharmacologic versus no prophylaxis	1 RCT (2 comp)	Yes	Significantly decreased risk, RR: 0.21 (0.05 to 0.95), NNT 19 to 22	L	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.26 (0.98 to 1.62)	M	L
KQ 4-8. PE					
Pharmacologic versus no prophylaxis	11 RCTs	Yes	No significant difference, OR 0.38 (0.13 to 1.07)	L	L
LMWH versus UFH	10 RCTs	Yes	Significantly decreased odds, OR 0.48 (0.24 to 0.95), NNT 8	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.18 (0.41 to 3.39)	M	L
LMWH versus VKA	5 RCTs	Yes	No significant difference, OR 1.11 (0.57 to 2.19)	M	M
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 3.23 (0.56 to 18.98)	L	L
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged versus standard duration prophylaxis	6 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.04 to 0.47), NNT 24 to 232	H	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80)		
KQ 4-8. Fatal PE					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.90 (0.38 to 2.13)	L	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, OR 1.43 (0.08 to 24.82)	L	L
KQ 4-8. Nonfatal PE					
Pharmacologic versus no prophylaxis	5 RCTs	Yes	No significant difference, OR 0.21 (0.04 to 1.30)	L	L
LMWH versus UFH	10 RCTs	Yes	No significant difference, OR 0.50 (0.25 to 1.00)	L	L
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.68 (0.34 to 1.37)	M	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, OR 0.93 (0.23 to 3.66)	L	L
LMWH versus VKA	3 RCTs	Yes	No significant difference, OR 1.00 (0.20 to 4.95)	L	L
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 3.27 (0.56 to 18.98)	L	L
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged versus standard duration prophylaxis	5 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.03 to 0.54), NNT 58	M	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)		
KQ 4-8. Mortality					
Pharmacologic versus no prophylaxis	9 RCTs 2 OBS	Yes (RCTs)	No significant difference, OR 1.23 (0.54 to 2.78). Observational data supported this finding.	L	L
LMWH versus UFH	8 RCTs	Yes	No significant difference, OR 0.39 (0.10 to 1.49)	M	L
LMWH versus FXI	4 RCTs 1 OBS	Yes (RCTs)	No significant difference, RCT: OR 1.08 (0.72 to 1.60); observational data suggests significantly higher percent of deaths in patients who received LMWH versus factor Xa inhibitors	M	L
LMWH versus DTI	4 RCTs	Yes	No significant difference, RR 0.45 (0.15 to 1.36)	M	L
LMWH versus VKA	6 RCTs	Yes	No significant difference, OR 0.79 (0.42 to 1.50)	M	M

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus mechanical	2 RCTs	Yes	No significant difference, OR 0.31 (0.05 to 1.80)	L	L
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 7.13 (0.74 to 68.80)	L	L
KQ 4-8. DVT					
Pharmacologic versus no prophylaxis	16 RCTs	Yes	Significantly decreased risk, RR: 0.55 (0.45 to 0.67), NNT 3 to 11	M	L
Antiplatelet versus mechanical	2 RCTs	Yes	Significantly increased risk, RR 1.63 (1.11 to 2.39), NNH 4 to 27	M	L
LMWH versus UFH	13 RCTs	Yes	Significantly decreased risk, RR 0.80 (0.65 to 0.99), NNT 12 to 100	M	L
	1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17)		
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, RR 2.06 (1.66 to 2.55), NNH 8 to 24	H	L
LMWH versus VKA	5 RCTs	Yes	Significantly decreased risk, RR 0.66 (0.55 to 0.79), NNT 6 to 13	L	M
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 0.90 (0.71 to 1.14)	M	L
UFH versus DTI	2 RCTs	Yes	Significantly increased risk, RR 2.31 (1.34 to 4.00), NNH 5 to 11	M	L
VKA versus mechanical	3 RCTs	Yes	No significant difference, RR 1.45 (0.75 to 2.82)	L	L
Enoxaparin versus other LMWH	2 RCTs	Yes	No significant difference, RR 1.05 (0.64 to 1.71)	L	L
IPC versus GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.06 (0.01 to 0.41), NNT 3 to 7	L	L
Pharmacologic + mechanical versus pharmacologic	3 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.32 to 0.72), NNT 3 to 67	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.09 (0.01 to 0.85), NNT 5		
Prolonged versus standard duration prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.37 (0.21 to 0.64), NNT 5 to 32	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)		
KQ 4-8. Asymptomatic DVT					
Pharmacologic versus no prophylaxis	3 RCTs	Yes	Significantly decreased risk, RR 0.52 (0.40 to 0.69), NNT 4 to 6	M	L
LMWH versus UFH	2 RCTs	Yes	No significant difference, RR 0.70 (0.43 to 1.16)	L	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 0.97 (0.85 to 1.10)	M	M
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.31 to 0.75), NNT 8 to 65	H	L
KQ 4-8. Symptomatic DVT					
Pharmacologic versus no prophylaxis	3 RCTs	Yes	No significant difference, OR 0.79 (0.17 to 3.73)	M	L
LMWH versus UFH	3 RCTs	Yes	No significant difference, OR 0.62 (0.22 to 1.75)	L	L
LMWH versus FXI	5 RCTs	Yes	No significant difference, OR 0.51 (0.22 to 1.21)	M	M
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 0.98 (0.34 to 2.87)	M	L
LMWH versus VKA	3 RCTs	Yes	No significant difference, OR 0.87 (0.61 to 1.24)	M	L
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased odds, OR 0.36 (0.16 to 0.81), NNT 27 to 79	H	M
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)		
KQ 4-8. Proximal DVT					
Pharmacologic versus no prophylaxis	11 RCTs	Yes	Significantly decreased risk, RR 0.53 (0.39 to 0.73), NNT 6 to 79	M	L
LMWH versus UFH	9 RCTs	Yes	Significantly decreased risk, RR 0.60 (0.38 to 0.93), NNT 14 to 50	H	L

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, OR 2.24 (1.55 to 3.24), NNH 43 to 83	M	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 0.91 (0.40 to 2.11)	L	M
LMWH versus VKA	6 RCTs	Yes	No significant difference, RR 0.63 (0.39 to 1.00)	L	M
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 0.65 (0.34 to 1.26)	M	L
UFH versus DTI	2 RCTs	Yes	Significantly increased odds, OR 4.74 (2.99 to 7.49), NNH 11	M	L
VKA versus mechanical	3 RCTs	Yes	Significantly decreased risk, RR 0.34 (0.16 to 0.73), NNT 11 to 31	M	L
Enoxaparin versus other LMWH	2 RCTs	Yes	No significant difference, RR 1.06 (0.62 to 1.81)	L	L
IPC versus GCS	2 RCTs	No	No significant difference, one trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.12 (0.01 to 1.99)	L	M
Pharmacologic + mechanical versus pharmacologic	3 RCTs	Yes	No significant difference, RR 0.33 (0.09 to 1.22)	L	M
	2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in 1 trial and RR 0.09 (0.01 to 0.85) in the other trial		
Pharmacologic + mechanical versus mechanical	2 RCTs	Yes	No significant difference, RR 0.78 (0.35 to 1.74)	L	L
Prolonged versus standard duration prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.29 (0.16 to 0.52), NNT 9 to 71	H	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)		
KQ 4-8. Distal DVT					
Pharmacologic versus no prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.38 to 0.82), NNT 7 to 25	M	L
LMWH versus UFH	8 RCTs	Yes	No significant difference, RR 0.95 (0.74 to 1.23)	H	L
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, RR 2.08 (1.72 to 2.52), NNH 10 to 31	H	L
LMWH versus VKA	2 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.43 to 0.73), NNT 6 to 10	M	L
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 1.00 (0.77 to 1.29)	M	L
IPC versus GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.07 (0.01 to 0.54), NNT 3 to 11	L	M
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons which were pooled to show RR 0.45 (0.16 to 1.26)	M	L
	1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29)		
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	No significant difference, RR 0.39 (0.15 to 1.04)	L	M
KQ 4-8. Major bleeding					
Pharmacologic versus no prophylaxis	7 RCTs	Yes	No significant difference, RR 0.74 (0.36 to 1.51)	M	L
LMWH versus UFH	7 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.37 to 0.88), NNT 41	H	L
LMWH versus FXI	4 RCTs 1 OBS	Yes (RCT)	Significantly decreased odds, RCT: OR 0.65 (0.48 to 0.89), NNT 74 to 145; observational data suggested no significant difference	M	L
LMWH versus DTI	4 RCTs	Yes	No significant difference, RR 1.12 (0.80 to 1.57)	M	L

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus VKA	7 RCTs	Yes	Significantly increased odds, OR 1.92 (1.27 to 2.91), NNH 57 to 220	H	M
	1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8		
Enoxaparin versus other LMWH	2 RCT	Yes	No significant difference, RR 1.98 (0.53 to 7.37)	M	L
Prolonged versus standard duration prophylaxis	5 RCTs	Yes	No significant difference, OR 2.18 (0.73 to 6.51)	L	L
KQ 4-8. Major bleeding leading to reoperation					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.67 (0.28 to 1.61)	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.27 (0.43 to 3.75)	M	L
UFH versus DTI	2 RCTs	No	No significant difference, one trial had no events and the remaining trial showed OR 0.51 (0.10 to 2.55)	L	L
KQ 4-8. Minor bleeding					
Pharmacologic prophylaxis versus no prophylaxis	5 RCTs	Yes	Significantly increased risk, RR 1.61 (1.12 to 2.32), NNH 4 to 166	H	M
LMWH versus UFH	5 RCTs	Yes	No significant difference, RR 0.90 (0.63 to 1.28)	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR: 1.07 (0.89 to 1.29)	M	L
LMWH versus VKA	7 RCTs	Yes	Significantly increased risk, RR 1.23 (1.06 to 1.43), NNH 18 to 218	M	M
	1 RCT (2 comp)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37)] on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8		
VKA versus mechanical	2 RCTs	Yes	No significant difference, OR 0.80 (0.26 to 2.41)	L	L
Prolonged versus standard duration prophylaxis	3 RCTs	Yes	Significantly increased odds, OR 2.44 (1.41 to 4.20), NNH 11 to 118	H	M
KQ 4-8. Surgical site bleeding					
LMWH versus UFH	3 RCTs	Yes	No significant difference, OR 0.92 (0.46 to 1.82)	L	L
LMWH versus VKA	2 RCT	Yes	Significantly increased odds OR 2.63 (1.31 to 5.28), NNH 23 to 64	L	L
Enoxaparin versus other LMWH	2 RCT	Yes	No significant difference, RR 1.35 (0.30 to 5.97)	L	L
KQ 4-8. Bleeding leading to transfusion					
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 1.00 (0.59 to 1.69)	H	L
KQ 4-8. HIT					
LMWH versus UFH	3 RCTs	Yes	Significantly decreased odds, OR 0.12 (0.03 to 0.43), NNT 34 to 202	M	L
KQ 4-8. Readmission					
LMWH versus UFH	2 RCT	Yes	No significant difference, RR 0.82 (0.20 to 3.38)	L	L
LMWH versus mechanical	2 RCT	Yes	No significant difference, OR 0.83 (0.22 to 3.11)	L	L
Prolonged versus standard duration prophylaxis	1 RCT (2 comp)	Yes	No significant difference, RR 0.29 (0.96 to 1.34)	L	L

* denotes that all base case analyses with at least 1 randomized controlled trial or 1 controlled observational study and a strength of evidence of low, moderate, or high evaluating the given outcome are represented in this table.

Table note: NA=Not Applicable; OR=Peto's Odds Ratio; RCT=Randomized Controlled Trial; RR=Relative Risk; DTI=direct thrombin inhibitor; FXI=factor Xa inhibitor; h=high; HFS=hip fracture surgery; L=low; LMWH=low molecular weight heparin; M=moderate; NA=Not Applicable; OBS=observational; OR=Peto's Odds Ratio; RCT=Randomized Controlled Trial; RR=Relative Risk; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VKA=vitamin K antagonist

Discussion

In the comparative effectiveness review of patients with major orthopedic surgery, DVT is still common in the absence of prophylaxis and PE and major bleeding outcomes also occur, although at lower rates. We do not have adequate data looking at the association between specific surgical or patient factors and the occurrence of health outcomes of interest. The impact of the intermediate outcome of DVT on final health outcomes such as PE cannot be determined with confidence. It is difficult to discriminate between DVT being causative for, or colinear with, the occurrence of PE given the available literature. The comparative balance of benefits to harms is favorable for providing pharmacologic prophylaxis and possibly for providing mechanical prophylaxis as well and providing longer term prophylaxis (28 days or longer) versus using only short term prophylaxis (7 to 10 days).

While there are advantages of LMWHs over UFH in terms of the balance of benefits to harms, the comparative balance for LMWHs versus other drug classes are harder to determine because there is a trade off between benefits and harms (better efficacy versus VKAs but higher bleeding; worse efficacy versus factor Xa antagonists but lower bleeding). Injectable UFH, is likely inferior to factor Xa inhibitors in the balance of benefits to harms as well. When we evaluated intraclass comparisons, the balance of benefits to harms for one LMWH versus another is similar and the balance for different mechanical modalities may be similar as well. However, we cannot determine if the balance of benefits to harms is favorable for combining pharmacologic and mechanical modalities of prophylaxis together versus simply using one modality alone.

There are numerous limitations to the current literature base. First, when we assess orthopedic surgeries other than THR, TKR and HFS, we do not have an adequate literature base to determine benefits or harms. Future studies comparing prophylactic strategies versus no prophylaxis are needed to discern if prophylaxis is needed in nonmajor orthopedic surgeries. While we found that there is a real risk of developing DVT, PE, and major bleeding with major orthopedic surgery, there is inadequate data to say whether or not DVT causes PE. We were not even able to determine that DVT is an independent predictor of PE which would be the next logical step to be assessed in a large observational study. Similarly, determining the impact of symptomatic and asymptomatic DVT on patient perceived quality of life could help determine the importance of this intermediate outcome. UFH should not be an initial prophylactic strategy in major orthopedic surgery since LMWHs have a better balance of benefits to harms but in general, whether one agent within the class should be used versus another is not clearly determined. Future direct comparative trials are needed but funding these trials could be difficult to conduct since aspirin, warfarin, and UFH are generically available. The large number of mechanical prophylactic devices available also makes it difficult to conduct a trial with strong applicability to all devices. In all cases, harms need to be determined because as we have suggested, in many comparisons between classes, there is a tradeoff between increased efficacy and increased bleeding. Future studies assessing the utility of dual prophylaxis versus single modality therapy is also needed.

Glossary

Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.
Deep Venous Thrombosis (DVT): A blood clot occurring in a leg vein and verified with Doppler ultrasound or venography. Proximal deep vein thrombosis was defined as blood clot occurring in either popliteal, femoral, or any deep veins of the pelvis. Distal vein thrombosis was defined as blood clot occurring distal to the popliteal vein in the calf veins of the leg. When both bilateral and unilateral clots data were available, unilateral clots data was used for the analysis.
DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.
Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.
Hip Fracture Surgery (HFS): The surgical procedure to treat hip fracture.
I^2: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to100.
Major Orthopedic Surgery: Total hip arthroplasty, total knee arthroplasty, hip fracture surgery
Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.
Other Orthopedic Surgery: knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or diskectomy all of the lumbar region).
Peto's Odds Ratio (OR): An odds ratio is the ratio of an event occurring in an exposed group to an event occurring in the nonexposed group in a given population. A ratio of one indicates no difference in the odds between the two groups. Peto's odds ratios are used to compare two groups when the number of events is rare.
Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.
Pulmonary Embolism (PE): A blood clot in the vasculature of the lung. In order to have a pulmonary embolism in our review, it needed to be verified with spiral computed tomography angiography or ventilation/perfusion scan with either Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for pulmonary embolism.
Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.
Sensitivity Analyses: A 'what if' analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.
Standard Deviations (SDs): A measure of the variability of a data set. For a simple data set with numbers, can be calculated using the following formula: $\sigma = ((\sum(x-x_m))^2/N)^{0.5}$ where σ is standard deviation, x_m is the average, $\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x, N is the total number of values.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis.
Total Hip Arthroplasty (THR): The surgical replacement of the hip.
Total Knee Arthroplasty (TKA): The surgical replacement of the knee.
Venous Thromboembolism (VTE): The occurrence of either a deep venous thrombosis or pulmonary embolism.

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Introduction

Background

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

The main limitation of pharmacologic venous thromboembolism prophylaxis is the risk of bleeding. Based on historical data major bleeding following total hip replacement and total knee replacement is estimated to be 1 to 3 percent.[1] Determining the incidence of major bleeding with pharmacologic thromboprophylaxis is complicated by the variability in the definitions used in published literature and paucity of data in control patients. Additionally, complications such as postoperative bleeding and hematoma formation are considered risk factors for the development of early onset prosthetic joint infections.[3,4] Reoperation is frequently required for debridement with or without removal of the infected prosthesis. Following removal of an infected prosthesis and extended intravenous antibiotic treatment further surgery may be required to either implant a new prosthesis or perform an arthrodesis of the joint.

There are many unknowns that need to be explored in a comparative effectiveness review. In contemporary practice, the risk of VTE, PE, and DVT and the causal link between DVT and PE has not been well established. In addition to major orthopedic surgery, there are a variety of other orthopedic surgeries and the impact of prophylaxis has not been well evaluated. While prophylactic strategies may decrease the risk of VTE, DVT, and PE, the magnitude of benefit in contemporary practice using rigorous definitions of endpoints and the impact of duration of prophylaxis on outcomes is not well delineated. Whether dual prophylactic strategies are superior to a single modality is not well defined. In addition, in order to determine comparative effectiveness, both the benefits and harms need to be appreciated. Finally, several previous meta-analyses and guidelines allowed the use of medications or devices that are not available for use in the United States reducing its applicability.

Objective

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

The Key Questions

Key Question 1.

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

Key Question 2.

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

Key Question 3.

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

Key Question 4.

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

Key Question 5.

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

Key Question 6.

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

Key Question 7.

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

Key Question 8.

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

Key Question 9.

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter placement compared to any external mechanical intervention on symptomatic objectively confirmed venous thromboembolism, major venous

thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, reoperation or IVC filter placement-associated insertion site thrombosis?

Key Question 10.

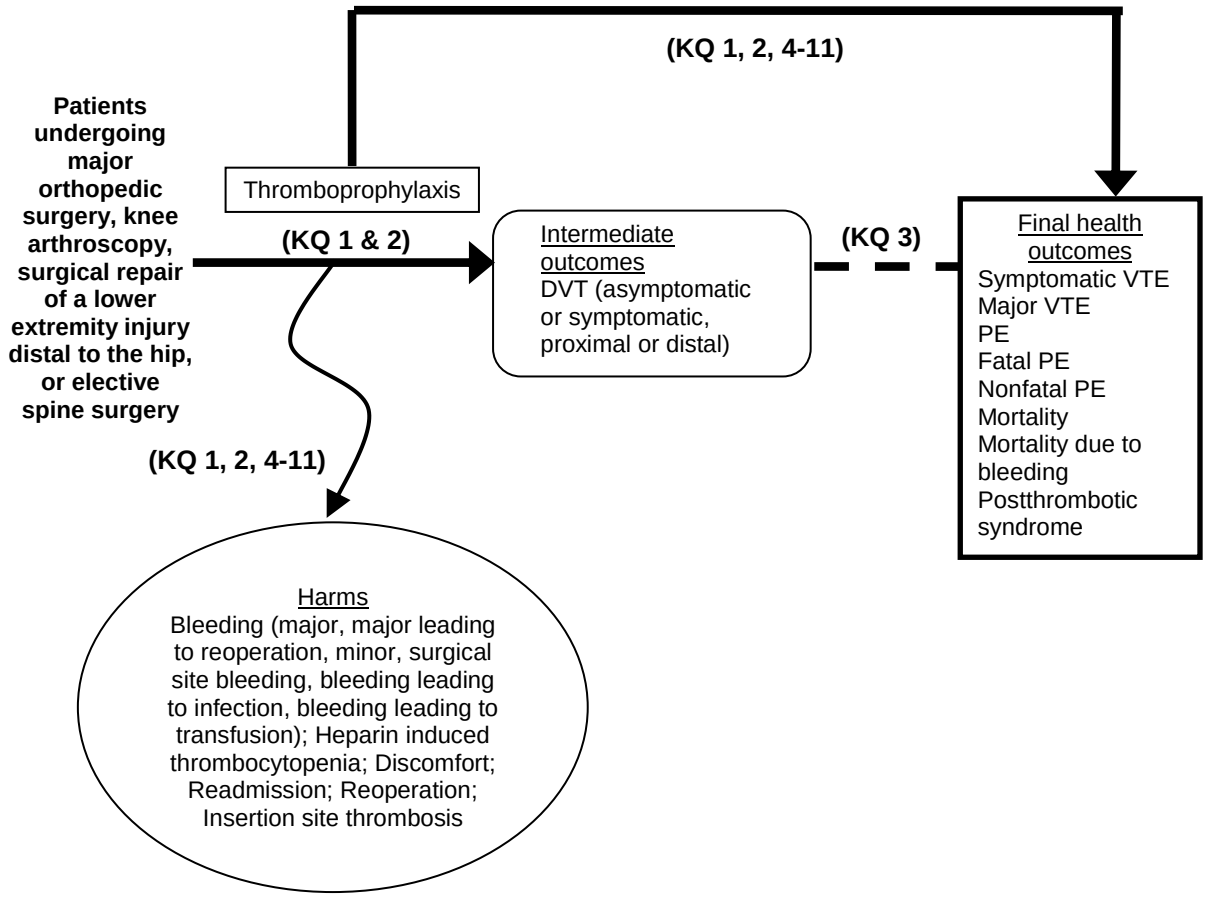
In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared to no thromboprophylaxis intervention on symptomatic objectively confirmed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

Key Question 11.

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

Analytic Framework

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



Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism
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Methods

Input from stakeholders

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

Searching for the evidence

Two independent investigators conducted systematic literature searches of Medline, The Cochrane Central Register of Controlled Trials, and Scopus from 1980 to the present. Language restrictions were not imposed. Two separate searches of these databases were conducted and the complete search strategies are included in Appendix A. The first search was used to identify studies which evaluated pharmacologic, mechanical, or inferior vena cava filter methods of thromboprophylaxis in patients undergoing major orthopedic surgery, described the association between patient, surgical, or postsurgical characteristics and venous thrombembolism or bleeding, or described the association between intermediate and final health outcomes to answer key questions 1 through 9. The second search was used to identify studies which evaluated pharmacologic or mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip or elective spine surgery to answer key questions 10 and 11. A manual search of references of clinical trials, meta-analyses, and systematic reviews was conducted. A grey literature search was conducted by the Scientific Resource Center and relevant citations were 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.

Inclusion and exclusion criteria

Two independent investigators assessed studies for inclusion in a parallel manner based on a priori defined criteria. In evaluating all key questions, randomized controlled trials of any size or controlled observational trials enrolling ≥ 750 patients were included if they explicitly reported

the use of imagining studies to confirm venous thrombomebolic events (Doppler ultrasound or venography for deep vein thrombosis and spiral computed tomography angiography or ventilation/perfusion scan with either Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria or high clinical suspicion based on symptoms for pulmonary embolism.[5,6] Observational studies were limited to those with a larger sample size given that most contemporary randomized controlled trials 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. Studies were included if the pharmacologic thromboprophylaxis agent to which patients were randomized had Federal Drug Administration approval for an indication and mechanical thromboprophylactic devices to which patients were randomized were available for use in the United States.

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

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

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

For key questions 4 through 9, studies were included if the study reported data on at least one prespecified outcome of interest. Additionally, for key question 4 only studies which compared pharmacologic or mechanical prophylaxis to placebo or control without the use of off protocol prophylaxis (with the exception of elastic stockings) were included. For key question 5, only studies which randomized patients into one pharmacologic or mechanical intervention versus another single intervention were included. For key question 7, only studies which randomized patients to a combination of pharmacologic plus mechanical prophylaxis versus one of the interventions alone were included.

Additional inclusion criteria for the evaluation of key questions 10 and 11 were 1) studies which included only patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament

reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or diskectomy all of the lumbar region) or reported separate results for these orthopedic surgeries; 2) compared pharmacologic or mechanical methods of thromboprophylaxis versus control or compared injectable antithrombotic agents (low molecular weight heparin, unfractionated heparin, factor Xa antagonists, direct thrombin inhibitors) to mechanical interventions; 4) studies which reported data on at least one prespecified outcome of interest.

Data extraction and data management

Two reviewers used a standardized data extraction tool to independently extract study data with disagreements resolved through discussion. (Appendix B) The following data was collected from each trial when applicable: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population (inclusion and exclusion criteria, geographic location, thromboprophylaxis intervention, length of study, duration of patient followup), patient baseline, surgical and postsurgical characteristics (including those which may modify risk of venous thromboembolism or bleeding), 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), 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 were contacted for clarification or to provide additional data when necessary. For pharmacologic methods of prophylaxis included in this report that were not yet approved for this indication by the Federal Drug Administration at the time of this report, data was extracted for the regimen which most closely resembled that from phase 3 clinical trials.

Assessment of methodological quality of individual studies

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

Table 1. Summary of rating of quality of individual studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; and clear reporting of dropouts.

Quality Rating	Definition
Fair	These studies are susceptible to some bias, but it is not sufficient to invalidate results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information, or discrepancies in reporting.

Data synthesis

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

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

The remaining key questions 4 through 11 explore the impact of thromboprophylaxis on final health outcomes, intermediate outcomes, and adverse effects. We qualitatively examined data from all identified studies. The base case analysis for each key question was in major orthopedic surgery (total hip replacement, total knee replacement, and hip fracture surgery). For each outcome, we conducted separate analyses of studies comparing each individual thromboprophylactic intervention with placebo or control and studies in which different thromboprophylactic interventions were compared to each other. Key questions 5 through 9 and 11 explore direct comparisons between or within specified classes and therefore only direct comparison trials were used in their quantitative analysis. In key questions 10 and 11, trials pertaining to each orthopedic surgery category (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery) were discussed separately due to the paucity of data which met inclusion criteria.

We conducted meta-analyses when two or more trials adequate for pooling were available for any outcome. Randomized controlled trials were pooled but data from observational studies were not. For dichotomous outcomes, weighted averages are reported as relative risks or Peto’s odds ratio with associated 95 percent confidence intervals. Peto’s odds ratio was chosen over relative risk when the control event rate was exceptionally low (less than 5 percent) and the number of

subjects randomized in each group of a trial was similar in the majority of trials within the given analysis.[7] As heterogeneity between included studies was expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating relative risks and 95 percent confidence intervals.[8] In the event that there was more than one method of thromboprophylaxis being compared with another method of thromboprophylaxis (i.e. low molecular weight heparin versus low molecular weight heparin plus compression stockings versus compression stockings), each method of thromboprophylaxis was compared individually against the other (as a separate trial) by dividing the control group equally between the comparisons.[8] The number needed to treat or number needed to harm was calculated for statistically significant results of the base case analysis for key questions 4 through 11 using the control event rate ranged and the observed pooled effect estimate.

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

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

Grading the strength of the evidence

We used the Evidence-based Practice Center Grading of Recommendations Assessment, Development guide to assess the strength of evidence.[9] This system uses four required domains; risk of bias, consistency, directness, and precision. Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. For study design, whether the study was a randomized controlled trial or an observational study was recorded. Studies were ranked as having no limitations, serious limitations, or very serious limitations. Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We assessed whether or not the effect sizes were on the same side of unity, whether the range of effect sizes was narrow, and the degree of statistical heterogeneity in evaluating consistency. We ranked this domain as no inconsistency, serious inconsistency, and very serious inconsistency. When only a single study is included, consistency cannot be judged. Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is

required to link interventions to the most important health outcomes. We ranked this domain as no indirectness, serious indirectness, and very serious indirectness. Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we evaluated the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

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

Table 2. Definitions for grading the strength of evidence

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

Evaluating the applicability of the evidence

Effectiveness studies met five of the following seven criteria: enrolled a primary care population, used less stringent eligibility criteria, assessed final health outcomes, allowed for adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention to treat analysis.[10] Studies which met less than five criteria were classified as efficacy trials and were deemed to have less applicability. In addition, factors identified in Table 3 were important when determining applicability and were extracted into evidence tables for every study. Given these inputs, the applicability of each study was determined as was the applicability for the body of evidence for the base case analysis of each comparison within a key question.

Table 3. Applicability considerations and data extracted

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

Results

Results of the literature search

Two literature searches were conducted as previously described in the methods. The first search was used to identify literature to answer key questions 1 through 9. Upon conducting this literature search, we retrieved 3,464 unique citations from the database search, 120 citations from a manual review of the literature, and two citations added manually from the gray literature search conducted by the Scientific Resource Center. After duplicate citations were removed, 2,925 citations remained. A total of 2,112 citations were excluded at the title and abstract level while 640 citations were excluded at the full text level (Appendix C). A total of 173 articles were found to match our inclusion criteria. A summary of search results is presented in Figure 2.

Of the 173 articles included in search one, 120 articles represented 97 unique randomized controlled trials (n = 44,214).[11-20,20-127] Fourteen articles represented 13 unique controlled observational studies (n = 480,241).[128-141] Further details regarding the included trials and studies are provided per key question for those included in answering the key question. The study characteristics and quality of randomized controlled trials and observational studies are included in Appendix D and the baseline and procedural characteristics of enrolled patients in these trials and studies are in Appendix E. A summary of the results for key questions 1 through 8 with strength of evidence rating of low, moderate, or high are presented in Table 4. Evaluations for key questions 9 through 11 had insufficient strength of evidence and are not included. Evidence tables for final and intermediate health outcomes and harms are presented in Appendix F.

Thirty nine articles represented 39 unique systematic reviews or meta-analyses.[142-180] Of these, five meta-analyses were deemed relevant for comparison to the results of key question 1 and are described in Table 5. [144,150,155,160,162] Nineteen meta-analyses were deemed relevant for comparison to other key questions and are described in

Table 6. The remaining systematic reviews and meta-analyses were used to manually search for additional literature which met our inclusion criteria.

The second literature search was used to identify literature to answer key questions 10 through 11. Upon conducting this literature search, we retrieved 529 unique citations from the database search and 24 citations from a manual review of the literature. After removal of duplicate citations, 517 citations remained. A total of 433 citations were excluded at the title and abstract level while 78 citations were excluded at the full text level (Appendix B). A total of six articles met our inclusion criteria. A summary of search results is presented in Figure 3. Of the six articles included in search two, two articles represented two unique randomized controlled trials (n = 235).[181,182] The trial characteristics and quality of the trials as well as the baseline and procedural characteristic of enrolled patients can be found in Appendicies D and E. Four articles represented three unique meta-analyses which were used to manually search for additional literature which met our inclusion criteria as well as to summarize findings pertinent to key questions 10 and 11.[183-186]

Figure 2. PRISMA flow diagram for search one

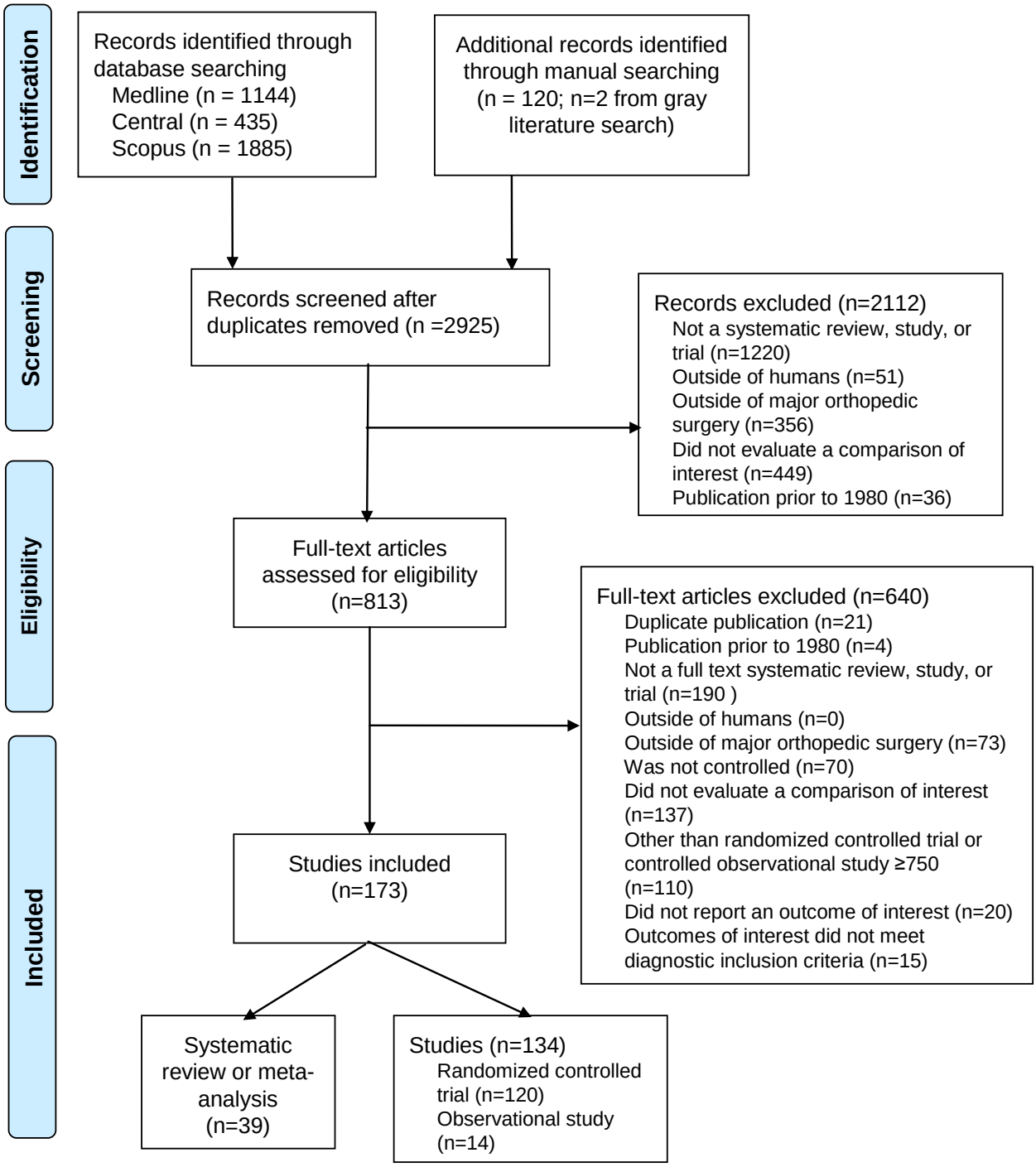

Figure 3. PRISMA flow diagram for search two

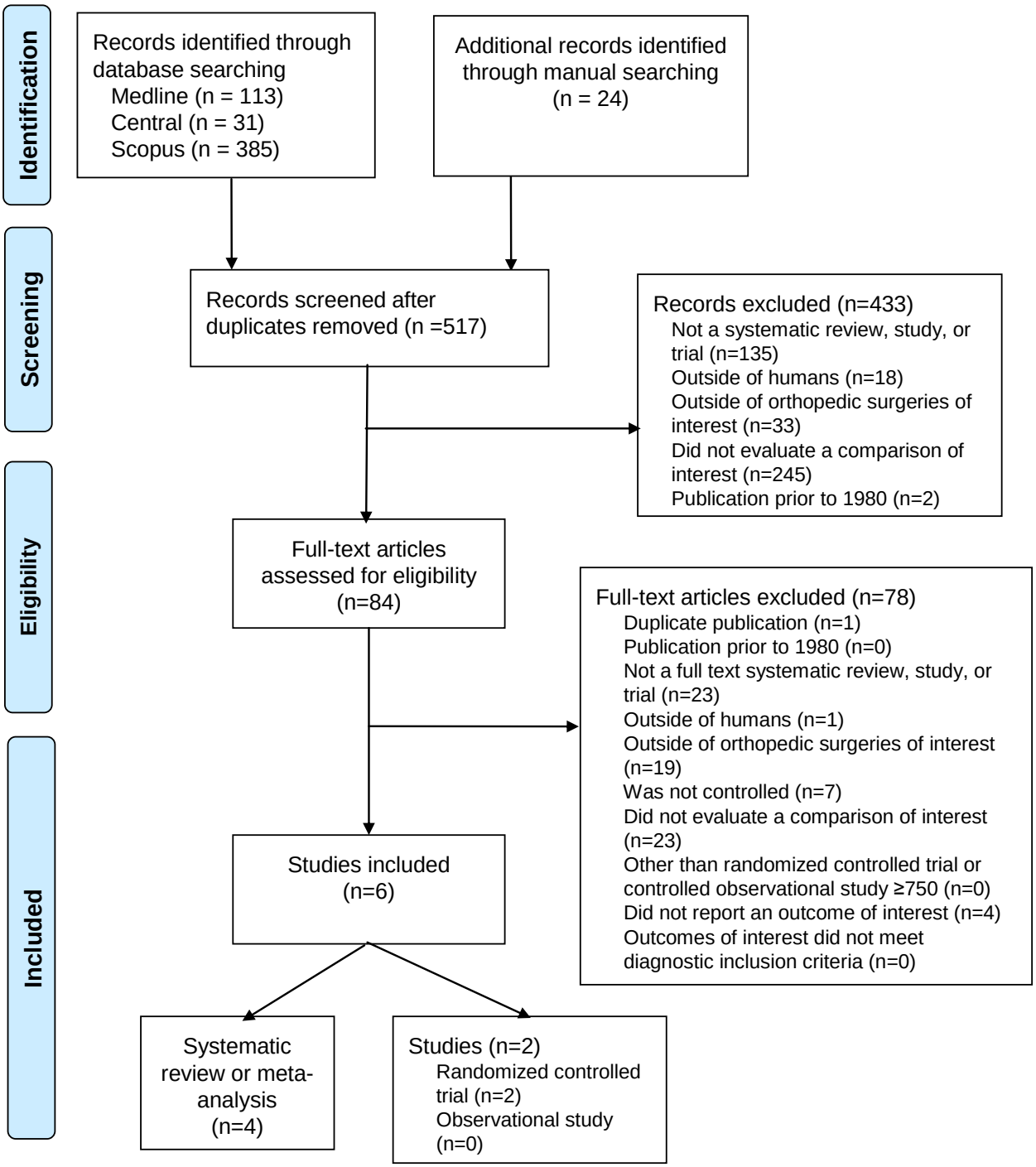

Table 4. Summary of results from base case analyses in patients who had major orthopedic surgery*

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ1. Incidence of health outcomes in total hip replacement					
PE	5 RCT	Yes	Pooled incidence of 6% (0.3% to 18%)	L	L
DVT	8 RCT	Yes	Pooled incidence of 39% (25% to 53%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 24%		
Proximal DVT	4 RCT	Yes	Pooled incidence of 32% (14% to 54%)	L	L
	1RCT	No	One trial not suitable for pooling had an incidence of 14%		
Distal DVT	2 RCT	Yes	Pooled incidence of 30% (4% to 68%)	L	L
	1 RCT	No	One trial not suitable for pooling had in incidence of 17.3%		
Major bleeding	5 RCT	Yes	Pooled incidence of 1% (0.2% to 3%)	M	L
Minor bleeding	5 RCT	Yes	Pooled incidence of 6% (1% to 16%)	L	M
KQ1. Incidence of health outcomes in total knee replacement					
PE	2 RCT	Yes	Pooled incidence of 1% (0.07% to 4%)	L	L
	1 OBS	No	The observational study had an incidence of 0.3%		
DVT	2 RCT	Yes	Pooled incidence of 46% (5% to 91%)	L	L
	1 RCT, 1 OBS	No	One trial not suitable for pooling had an incidence of 68.8% and the observational study had an incidence of 0%		
Proximal DVT	2 RCT	Yes	Pooled incidence of 17% (1% to 66%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 18.8%		
Distal DVT	2 RCT	Yes	Pooled incidence of 22% (12% to 35%)	L	L
	1 RCT	No	One trial not suitable for pooling had an incidence of 40.6%		
Major bleeding	2 RCT	Yes	Pooled incidence of 3% (0.2% to 8%)	L	L
Minor bleeding	2 RCT	Yes	Pooled incidence of 5% (3% to 8%)	M	L
KQ2. Impact of surgical characteristics on outcomes					
General versus regional anesthesia					
DVT	4 RCT, 2 OBS	No	The majority of trials showed that regional anesthesia was associated with a decrease in the risk of DVT while observational data was conflicting.	L	L
Symptomatic DVT	2 RCT	No	No significant difference	L	L
Proximal DVT	5 RCT	No	No significant difference	L	L
Cemented versus non cemented arthroplasty					
DVT	2 RCT, 3 OBS	No	No significant difference	L	L
pDVT	2 RCT	No	No significant difference	L	L
KQ2. Impact of patient characteristics on outcomes					
Congestive heart failure					
Symptomatic objectively confirmed VTE	2 OBS	No	Significantly increases odds	M	M
Age					

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
Symptomatic objectively confirmed VTE	2 OBS	No	No significant impact	L	M
DVT	3 OBS	No	Significantly increased risk	L	L
KQ4-8. Symptomatic objectively confirmed VTE					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.71 (0.49 to 1.04)	L	M
LMWH versus VKA	2 RCTs	Yes	No significant difference, OR 1.00 (0.69 to 1.46)	L	M
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.38 (0.19 to 0.77), NNT 8 to 54	M	L
KQ4-8. Major VTE					
Pharmacologic versus no prophylaxis	1 RCT (2 comp)	Yes	Significantly decreased risk, RR: 0.21 (0.05 to 0.95), NNT 19 to 22	L	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.26 (0.98 to 1.62)	M	L
KQ4-8. PE					
Pharmacologic versus no prophylaxis	11 RCTs	Yes	No significant difference, OR 0.38 (0.13 to 1.07)	L	L
LMWH versus UFH	10 RCTs	Yes	Significantly decreased odds, OR 0.48 (0.24 to 0.95), NNT 8	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.18 (0.41 to 3.39)	M	L
LMWH versus VKA	5 RCTs	Yes	No significant difference, OR 1.11 (0.57 to 2.19)	M	M
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 3.23 (0.56 to 18.98)	L	L
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged versus standard duration prophylaxis	6 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.04 to 0.47), NNT 24 to 232	H	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80)		
KQ4-8. Fatal PE					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.90 (0.38 to 2.13)	L	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, OR 1.43 (0.08 to 24.82)	L	L
KQ4-8. Nonfatal PE					
Pharmacologic versus no prophylaxis	5 RCTs	Yes	No significant difference, OR 0.21 (0.04 to 1.30)	L	L
LMWH versus UFH	10 RCTs	Yes	No significant difference, OR 0.50 (0.25 to 1.00)	L	L
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.68 (0.34 to 1.37)	M	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, OR 0.93 (0.23 to 3.66)	L	L
LMWH versus VKA	3 RCTs	Yes	No significant difference, OR 1.00 (0.20 to 4.95)	L	L
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 3.27 (0.56 to 18.98)	L	L
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34)	L	M
Prolonged versus standard duration prophylaxis	5 RCTs	Yes	Significantly decreased odds, OR 0.13 (0.03 to 0.54), NNT 58	M	L
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)		
KQ4-8. Mortality					
Pharmacologic versus no prophylaxis	9 RCTs 2 OBS	Yes (RCTs)	No significant difference, OR 1.23 (0.54 to 2.78). Observational data supported this finding.	L	L
LMWH versus UFH	8 RCTs	Yes	No significant difference, OR 0.39 (0.10 to 1.49)	M	L
LMWH versus FXI	4 RCTs 1 OBS	Yes (RCTs)	No significant difference, RCT: OR 1.08 (0.72 to 1.60); observational data suggests significantly higher percent of deaths in patients who received LMWH versus factor Xa inhibitors	M	L
LMWH versus DTI	4 RCTs	Yes	No significant difference, RR 0.45 (0.15 to 1.36)	M	L
LMWH versus VKA	6 RCTs	Yes	No significant difference, OR 0.79 (0.42 to 1.50)	M	M

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus mechanical	2 RCTs	Yes	No significant difference, OR 0.31 (0.05 to 1.80)	L	L
UFH versus DTI	2 RCTs	Yes	No significant difference, OR 7.13 (0.74 to 68.80)	L	L
KQ 4-8. DVT					
Pharmacologic versus no prophylaxis	16 RCTs	Yes	Significantly decreased risk, RR: 0.55 (0.45 to 0.67), NNT 3 to 11	M	L
Antiplatelet versus mechanical	2 RCTs	Yes	Significantly increased risk, RR 1.63 (1.11 to 2.39), NNH 4 to 27	M	L
LMWH versus UFH	13 RCTs	Yes	Significantly decreased risk, RR 0.80 (0.65 to 0.99), NNT 12 to 100	M	L
	1 RCT (2 comp)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17)		
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, RR 2.06 (1.66 to 2.55), NNH 8 to 24	H	L
LMWH versus VKA	5 RCTs	Yes	Significantly decreased risk, RR 0.66 (0.55 to 0.79), NNT 6 to 13	L	M
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 0.90 (0.71 to 1.14)	M	L
UFH versus DTI	2 RCTs	Yes	Significantly increased risk, RR 2.31 (1.34 to 4.00), NNH 5 to 11	M	L
VKA versus mechanical	3 RCTs	Yes	No significant difference, RR 1.45 (0.75 to 2.82)	L	L
Enoxaparin versus other LMWH	2 RCTs	Yes	No significant difference, RR 1.05 (0.64 to 1.71)	L	L
IPC versus GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.06 (0.01 to 0.41), NNT 3 to 7	L	L
Pharmacologic + mechanical versus pharmacologic	3 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.32 to 0.72), NNT 3 to 67	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.09 (0.01 to 0.85), NNT 5		
Prolonged versus standard duration prophylaxis	7 RCTs	Yes	Significantly decreased risk, RR 0.37 (0.21 to 0.64), NNT 5 to 32	M	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)		
KQ 4-8. Asymptomatic DVT					
Pharmacologic versus no prophylaxis	3 RCTs	Yes	Significantly decreased risk, RR 0.52 (0.40 to 0.69), NNT 4 to 6	M	L
LMWH versus UFH	2 RCTs	Yes	No significant difference, RR 0.70 (0.43 to 1.16)	L	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 0.97 (0.85 to 1.10)	M	M
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.31 to 0.75), NNT 8 to 65	H	L
KQ 4-8. Symptomatic DVT					
Pharmacologic versus no prophylaxis	3 RCTs	Yes	No significant difference, OR 0.79 (0.17 to 3.73)	M	L
LMWH versus UFH	3 RCTs	Yes	No significant difference, OR 0.62 (0.22 to 1.75)	L	L
LMWH versus FXI	5 RCTs	Yes	No significant difference, OR 0.51 (0.22 to 1.21)	M	M
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 0.98 (0.34 to 2.87)	M	L
LMWH versus VKA	3 RCTs	Yes	No significant difference, OR 0.87 (0.61 to 1.24)	M	L
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	Significantly decreased odds, OR 0.36 (0.16 to 0.81), NNT 27 to 79	H	M
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)		
KQ 4-8. Proximal DVT					
Pharmacologic versus no prophylaxis	11 RCTs	Yes	Significantly decreased risk, RR 0.53 (0.39 to 0.73), NNT 6 to 79	M	L
LMWH versus UFH	9 RCTs	Yes	Significantly decreased risk, RR 0.60 (0.38 to 0.93), NNT 14 to 50	H	L

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, OR 2.24 (1.55 to 3.24), NNH 43 to 83	M	L
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 0.91 (0.40 to 2.11)	L	M
LMWH versus VKA	6 RCTs	Yes	No significant difference, RR 0.63 (0.39 to 1.00)	L	M
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 0.65 (0.34 to 1.26)	M	L
UFH versus DTI	2 RCTs	Yes	Significantly increased odds, OR 4.74 (2.99 to 7.49), NNH 11	M	L
VKA versus mechanical	3 RCTs	Yes	Significantly decreased risk, RR 0.34 (0.16 to 0.73), NNT 11 to 31	M	L
Enoxaparin versus other LMWH	2 RCTs	Yes	No significant difference, RR 1.06 (0.62 to 1.81)	L	L
IPC versus GCS	2 RCTs	No	No significant difference, one trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.12 (0.01 to 1.99)	L	M
Pharmacologic + mechanical versus pharmacologic	3 RCTs	Yes	No significant difference, RR 0.33 (0.09 to 1.22)	L	M
	2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in 1 trial and RR 0.09 (0.01 to 0.85) in the other trial		
Pharmacologic + mechanical versus mechanical	2 RCTs	Yes	No significant difference, RR 0.78 (0.35 to 1.74)	L	L
Prolonged versus standard duration prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.29 (0.16 to 0.52), NNT 9 to 71	H	M
	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)		
KQ 4-8. Distal DVT					
Pharmacologic versus no prophylaxis	6 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.38 to 0.82), NNT 7 to 25	M	L
LMWH versus UFH	8 RCTs	Yes	No significant difference, RR 0.95 (0.74 to 1.23)	H	L
LMWH versus FXI	4 RCTs	Yes	Significantly increased risk, RR 2.08 (1.72 to 2.52), NNH 10 to 31	H	L
LMWH versus VKA	2 RCTs	Yes	Significantly decreased risk, RR 0.56 (0.43 to 0.73), NNT 6 to 10	M	L
LMWH versus mechanical	3 RCTs	Yes	No significant difference, RR 1.00 (0.77 to 1.29)	M	L
IPC versus GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.07 (0.01 to 0.54), NNT 3 to 11	L	M
Pharmacologic + mechanical versus pharmacologic	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons which were pooled to show RR 0.45 (0.16 to 1.26)	M	L
	1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29)		
Prolonged versus standard duration prophylaxis	4 RCTs	Yes	No significant difference, RR 0.39 (0.15 to 1.04)	L	M
KQ 4-8 Major bleeding					
Pharmacologic versus no prophylaxis	7 RCTs	Yes	No significant difference, RR 0.74 (0.36 to 1.51)	M	L
LMWH versus UFH	7 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.37 to 0.88), NNT 41	H	L
LMWH versus FXI	4 RCTs 1 OBS	Yes (RCT)	Significantly decreased odds, RCT: OR 0.65 (0.48 to 0.89), NNT 74 to 145; observational data suggested no significant difference	M	L
LMWH versus DTI	4 RCTs	Yes	No significant difference, RR 1.12 (0.80 to 1.57)	M	L

Endpoint / Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
LMWH versus VKA	7 RCTs	Yes	Significantly increased odds, OR 1.92 (1.27 to 2.91), NNH 57 to 220	H	M
	1 RCT (2 comp)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8		
Enoxaparin versus other LMWH	2 RCT	Yes	No significant difference, RR 1.98 (0.53 to 7.37)	M	L
Prolonged versus standard duration prophylaxis	5 RCTs	Yes	No significant difference, OR 2.18 (0.73 to 6.51)	L	L
KQ 4-8 Major bleeding leading to reoperation					
LMWH versus FXI	4 RCTs	Yes	No significant difference, OR 0.67 (0.28 to 1.61)	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR 1.27 (0.43 to 3.75)	M	L
UFH versus DTI	2 RCTs	No	No significant difference, one trial had no events and the remaining trial showed OR 0.51 (0.10 to 2.55)	L	L
KQ 4-8 Minor bleeding					
Pharmacologic prophylaxis versus no prophylaxis	5 RCTs	Yes	Significantly increased risk, RR 1.61 (1.12 to 2.32), NNT 4 to 166	H	M
LMWH versus UFH	5 RCTs	Yes	No significant difference, RR 0.90 (0.63 to 1.28)	M	L
LMWH versus DTI	3 RCTs	Yes	No significant difference, RR: 1.07 (0.89 to 1.29)	M	L
LMWH versus VKA	7 RCTs	Yes	Significantly increased risk, RR 1.23 (1.06 to 1.43), NNH 18 to 218	M	M
	1 RCT (2 comp)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37)] on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8		
VKA versus mechanical	2 RCTs	Yes	No significant difference, OR 0.80 (0.26 to 2.41)	L	L
Prolonged versus standard duration prophylaxis	3 RCTs	Yes	Significantly increased odds, OR 2.44 (1.41 to 4.20), NNH 11 to 118	H	M
KQ 4-8 Surgical site bleeding					
LMWH versus UFH	3 RCTs	Yes	No significant difference, OR 0.92 (0.46 to 1.82)	L	L
LMWH versus VKA	2 RCT	Yes	Significantly increased odds OR 2.63 (1.31 to 5.28), NNH 23 to 64	L	L
Enoxaparin versus other LMWH	2 RCT	Yes	No significant difference, RR 1.35 (0.30 to 5.97)	L	L
KQ 4-8 Bleeding leading to transfusion					
LMWH versus DTI	2 RCTs	Yes	No significant difference, RR 1.00 (0.59 to 1.69)	H	L
KQ 4-8 HIT					
LMWH versus UFH	3 RCTs	Yes	Significantly decreased odds, OR 0.12 (0.03 to 0.43), NNT 34 to 202	M	L
KQ 4-8 Readmission					
LMWH versus UFH	2 RCT	Yes	No significant difference, RR 0.82 (0.20 to 3.38)	L	L
LMWH versus mechanical	2 RCT	Yes	No significant difference, OR 0.83 (0.22 to 3.11)	L	L
Prolonged versus standard duration prophylaxis	1 RCT (2 comp)	Yes	No significant difference, RR 0.29 (0.96 to 1.34)	L	L

* denotes that all base case analyses with at least 1 randomized controlled trial or 1 controlled observational study and a strength of evidence of low, moderate, or high evaluating the given outcome are represented in this table.

Abbreviations: NA=Not Applicable; OR=Peto's Odds Ratio; RCT=Randomized Controlled Trial; RR=Relative Risk; DTI=direct thrombin inhibitor; FXI=factor Xa inhibitor; h=high; HFS=hip fracture surgery; L=low; LMWH=low molecular weight heparin; M=moderate; NA=Not Applicable; OBS=observational; OR=Peto's Odds Ratio; RCT=Randomized Controlled Trial; RR=Relative Risk; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VKA=vitamin K antagonists

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

Author, Year	N studies (N participants)	Population	Outcome and pooled incidence / risk in placebo or control arms (confidence interval)
Brookenthal, 2001[144]	14 (3482)	TKA	Symptomatic PE: AR 0% (0 to 10.9%) Fatal PE: AR 0% (0% to 4.2%)* DVT: AR 60.2% (55.7% to 64.5%)
Freedman, 2000[150]	52 (10,929)	THA	Symptomatic PE: AR 1.51% (0.81% to 2.57%) Fatal PE: AR 0% (0% to 43%) DVT: AR 48.5% (43.4% to 53.7%) pDVT: AR 25.8% (21.4% to 30.7%) dDVT: AR 22.4% (18.8% to 26.6%) Major Bleeding: AR 0.56% (0.15% to 1.43%) Minor Bleeding: AR 3.0% (1.1% to 8.2%)
Murray, 1996[162]	181 papers (930,000)	THA	Fatal PE: 12% (3% to 30%)*
Imperiale, 1994[155]	56 (NR)	THA	DVT: 47% (40% to 53%)† pDVT: 23% (17% to 29%)† PE: 2.4% (1.3% to 3.5%)†
Mohr, 1993[160]	21 (3052)	THA	DVT: WMR 50% (NR) pDVT: WMR 24% (NR)

* rates with 95% confidence interval using Poisson distribution
† unadjusted pooled risk

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

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

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Friedman, 2010[176]	3 (8,210)	Population: THA and TKA Intervention 1: Dabigatran 220mg po QD Intervention 2: Dabigatran 150mg po QD Intervention 3: Enoxaparin 40mg SQ QD or 30mg SQ BID	---	---	Dabigatran 220mg versus enoxaparin Major bleeding: RD -0.2% (-0.8 to 0.5) Dabigatran 150mg versus enoxaparin Major bleeding: RD -0.4% (-1.0 to 0.2)
Tasker, 2010[170]	5 (1,847)	Population: THR Intervention: LMWH Comparator: Placebo	Nonfatal PE: OR 0.14 (0.03 to 0.74) Mortality: OR 0.77 (0.15 to 3.99)	---	Major bleeding: OR 0.74 (0.23 to 2.4)
Hu, 2009[153]	21 (NR)	Population: THR and TKR Intervention: RA Comparator: GA	PE: OR 0.46 (0.21 to 1.02) Mortality: OR 0.94 (0.14 to 6.52)	DVT: OR 0.45 (0.24 to 0.84)	----
Wolowacz, 2009*[173]	3 (8,210)	Population: THA and TKA Intervention: Dabigatran 220mg po QD Comparator: Enoxaparin 40mg SQ QD or 30mg SQ BID	VTE: RR 0.94 (0.61 to 1.44)	---	Major bleeding: RR 0.94 (0.51 to 1.75)

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Mismetti, 2004[159]	29 (NR)	Population: THR, TKR, and HFS Intervention 1: VKA Intervention 2: Antiplatelet agent Intervention 4: IPC Intervention 5: UFH Intervention 6: LMWH Intervention 7: Placebo/control	VKA versus placebo/control PE: RR 0.23 (0.09 to 0.59) Death: RR 0.78 (0.56 to 1.09) VKA versus IPC Death: RR 1.58 (0.21 to 11.7) VKA versus UFH PE: RR 0.09 (0.004 to 2.40) VKA versus LMWH PE: RR 1.10 (0.59 to 2.05) Death: RR 1.30 (0.72 to 2.36)	VKA versus placebo/control DVT: RR 0.56 (0.37 to 0.84) VKA versus antiplatelet DVT: RR 0.84 (0.55 to 1.28) pDVT: RR 1.15 (0.67 to 1.98) VKA versus IPC aDVT: RR 1.21 (0.88 to 1.66) pDVT: RR 0.46 (0.25 to 0.82) VKA versus UFH aDVT: RR 1.25 (0.87 to 1.81) VKA versus LMWH DVT: RR 1.51 (1.27 to 1.79) pDVT: RR 1.51 (1.04 to 2.17)	VKA versus placebo/control Major Hemorrhage: RR 1.53 (0.68 to 3.45) VKA versus antiplatelet Major Hemorrhage: RR 0.98 (0.04 to 25) VKA versus IPC Major Hemorrhage: RR 1.77 (0.14 to 23) VKA versus LMWH Major Hemorrhage: RR 0.78 (0.49 to 1.26)
Muntz, 2004[161]	21 (20,523)	Population: THR, TKR, or HFS Intervention 1: LMWH Intervention 2: VKAs (warfarin and other coumarin derivatives) Intervention 3: UFH	---	---	VKAs versus LMWH Major Bleeding: RR 0.59 (0.44 to 0.80) UFH versus LMWH Major Bleeding: RR 1.52 (1.04 to 2.23)

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Turpie, 2004[180] and 2002[171]	4 (7,344)	Population: TKR, THR and HFS Intervention: Fondaparinux 2.5mg SQ QD Comparator: Enoxaparin (approved regimens)	VTE: Odds reduction: 49.6% (27.3 to 65.5) VTE: Odds reduction: 48.0% (27.3 to 63.2)	pDVT: Odds reduction: 57.4% (35.6 to 72.3)	
O'Donnell, 2003[165]	2 (907)† 5 (1,917) 7 (2,425)	Population: THA Intervention 1: Extended LMWH therapy after completion of an initial 7 to 12 days of prophylaxis after surgery Intervention 2: placebo/control	sVTE (3m): OR 0.39 (0.14 to 1.11) sPE (3m): ARR 0.36% (-.3% to 1.36%) Fatal PE (3m): ARR 0.09% (-0.08% to 0.27%)	---	---
Zufferey, 2003[175]	13 (1,925)	Population: THR, TKR, and HFS Intervention: LMWH (3000 anti-Xa IU to 6000 anti-Xa IU daily) Comparator: Placebo	---	aDVT: RR 0.51 (0.45 to 0.59)	Major hemorrhage: RR 0.80 (0.36 to 1.79)

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Handoll, 2002‡[151]	31 (2,958)	Population: HFS Intervention 1: LMWH Intervention 2: UFH Intervention 3: LMWH or UFH Intervention 4: Mechanical methods (IPC and VFP) Intervention 5: Placebo or control	LMWH or UFH versus placebo/control PE: RR 1.00 (0.49 to 2.02) Nonfatal PE: RR 4.94 (1.10 to 22.07) Fatal PE: RR 0.47 (0.19 to 1.14) Death: RR 1.16 (0.77 to 1.74) Mechanical versus control PE: RR 0.40 (0.17 to 0.96) Fatal PE: RR 0.27 (0.07 to 1.08) Death: RR 0.50 (0.22 to 1.14) LMWH versus UFH PE: RR 3.29 (0.82 to 13.32) Nonfatal PE: RR 12.42 (0.72 to 213.88) Death: RR 0.85 (0.31 to 2.36)	LMWH or UFH versus placebo/control DVT: RR 0.60 (0.50 to 0.71) pDVT: RR 0.45 (0.28 to 0.73) dDVT: RR 0.65 (0.47 to 0.89) UFH versus placebo/control DVT: OR 0.41 (0.30 to 0.56) Mechanical versus control DVT: RR 0.31 (0.19 to 0.51) pDVT: RR 0.22 (0.10 to 0.53) dDVT: RR 0.45 (0.23 to 0.85) LMWH versus UFH DVT: RR 0.67 (0.48 to 0.94) pDVT: RR 0.84 (0.47 to 1.48) dDVT: RR 0.68 (0.23 to 2.00)	---
Cohen, 2001[177]	6 (NR)	Population: Hip or knee arthroplasty Intervention: LMWH or warfarin followed by additional LMWH prophylaxis (total 4-5 weeks) Comparator: LMWH or warfarin (7-15 d) followed by placebo	VTE: OR 0.50 (0.30 o 0.83)	---	---

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Eikelboom, 2001[147]	9 (3,999)	Population: THR and TKR Intervention: Extended-duration prophylaxis with LMWH or UFH (30d-42d) Comparator: Standard-duration prophylaxis with LMWH or UFH	PE: OR 0.43 (0.17 to 1.06) Death: OR 0.68 (0.25 to 1.88)	sDVT: OR 0.41 (0.24 to 0.68) aDVT: OR 0.48 (0.36 to 0.63)	Major bleeding: OR 0.62 (0.22 to 1.75) Minor bleeding: OR 1.56 (1.08 to 2.26)
Hull, 2001[154]	6 (1,953)	Population: Elective hip arthroplasty Intervention: LMWH in and out of hospital Comparator: LMWH inhospital then placebo	---	DVT: RR 0.41 (0.32 to 0.54) pDVT: RR 0.31 (0.20 to 0.47) sDVT: RR 0.36 (0.20 to 0.67)	---

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Westrich, 2000[172]	23 (6,001)	Population: TKA Intervention 1: ASA 325mg to 650mg po QD Intervention 2: Warfarin (PT 1.3 to 1.5 of normal) Intervention 3: LMWH Intervention 4: IPC	ASA versus warfarin aPE: OR 1.2 (NR) sPE: OR 2.1 (0.9 to 4.8) ASA versus LMWH sPE: OR 2.7 (0.5 to 14) ASA versus IPC aPE: OR 2.5 (1.7 to 3.8) sPE: OR 6.5 (0.4 to 106) Warfarin versus LMWH sPE: OR 1.8 (0.2 to 14) Warfarin versus IPC aPE: OR 1.7 (1.1 to 2.6) sPE:OR 3.0 (0.2 to 53) LMWH versus IPC sPE: OR 2.4 (0.1 to 59)	ASA versus warfarin DVT: OR 1.7 (1.5 to 1.9) ASA versus LMWH DVT: OR 3.47 (3.04 to 3.96) ASA versus IPC DVT: OR 3.2 (2.7 to 3.8) Warfarin versus LMWH DVT: OR 2.05 (1.76 to 2.39) Warfarin versus IPC DVT: OR 1.9 (1.6 to 2.3) LMWH versus IPC DVT: OR 1.09 (0.9 to 1.33)	---
Howard, 1998[152]	10 (3,079)	Population: TKA Intervention 1: LMWH Intervention 2: Warfarin Intervention 3: UFH Intervention 4: Placebo	---	LMWH versus placebo DVT: RR 0.42 (0.26 to 0.67) pDVT: RR 0.11 (0.03 to 0.40) LMWH versus warfarin DVT: RR 0.71 (0.64 to 0.80) pDVT: RR 0.67 (0.43 to 1.04) LMWH versus UFH DVT: RR 0.76 (0.60 to 0.95) pDVT: RR 0.32 (0.13 to 0.80)	---

Author, Year	N studies (N subjects)	Population and Interventions	Final Health Outcomes	Intermediate Outcomes	Adverse outcomes
Anderson, 1993[143]	6 (1,420)	Population: THA Intervention: LMWH Comparator: UFH	sPE: OR 0.22 (0.05 to 0.88)	DVT: OR 0.72 (0.53 to 0.95) pDVT: OR 0.40 (0.28 to 0.59) dDVT: OR 1.21 (0.86 to 1.74)	Major bleeding: OR 0.64 (0.34 to 1.23) Minor bleeding: OR 0.92 (0.61 to 1.33)
Leizorovicz, 1992[179]	23 (3,976)§ 5 (595) 14 (2,692)	Population: Elective or non-elective orthopedic surgery Intervention 1: LMWH SQ QD Intervention 2: UFH Intervention 3: Placebo	LMWH versus placebo PE: OR 0.64 (0.08 to 5.03) Mortality: OR 0.92 (0.18 to 4.62) LMWH versus UFH PE: OR 0.53 (0.27 to 1.03) Mortality: OR 0.88 (0.37 to 2.07)	LMWH versus placebo DVT: OR 0.32 (0.22 to 0.46) LMWH versus UFH DVT: OR 0.83 (0.68 to 1.02)	LMWH versus placebo Bleeding: OR 0.69 (0.22 to 2.11) LMWH versus UFH Bleeding: OR 1.09 (0.76 to 1.58)
Nurmohamed, 1992[178]	6 (1,294)	Population: Elective or traumatic hip surgery Intervention: LMWH Comparator: UFH	PE: RR 0.43 (0.22 to 0.82)	DVT: RR 0.68 (0.54 to 0.86)	Major bleeding: RR 0.75 (0.26 to 2.14)

* results of random effects model
† the number of studies and subjects varied based on the outcome reported and follows this order: sVTE, sPE, fatal PE
‡ results are presented with 99% confidence intervals
§ the number of studies and subjects varied based on the comparison and follows this order: LMWH versus placebo, LMWH versus UFH

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

Key Question 1

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

Key Points

- The impact of orthopedic surgery on pulmonary embolism, deep vein thrombosis, and bleeding is most extensively evaluated in clinical trials for total hip replacement followed by total knee replacement and then hip fracture surgery. To determine the impact of surgery on venous thromboembolism, pulmonary embolism, or deep vein thrombosis we only allowed trial arms where no prophylaxis was given (either control or placebo) but for bleeding outcomes we also allowed trial arms with mechanical prophylaxis since the risk of bleeding is not impacted by these methods.
- Only evaluating trials and studies conducted from 1980 to the present limits the available literature base but likely reflects more contemporary practice. Only evaluating trials and studies with rigorous definitions of pulmonary embolism and deep vein thrombosis limits the available literature base and decreases the number of events that might be reported through the use of laxer definitions.
- We still had high statistical heterogeneity between trials for most endpoints which likely reflects the different time periods of followup, the countries and ethnicities where the trials were conducted in and when or how rigorously the endpoints were assessed for.
- In total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, respectively, the incidence of pulmonary embolism (6 percent, 1 percent, 3 percent), deep vein thrombosis (39 percent, 53 percent, 47 percent), proximal deep vein thrombosis (32 percent, 17 percent, --), distal deep vein thrombosis (30 percent, 30 percent, --), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (6 percent, 5 percent, --) major bleeding leading to reoperation (0 percent, 0 percent, --), and major bleeding leading to transfusion (0 percent, 0 percent, ---) are reported in clinical trials. While the incidence of deep vein thrombosis events is relatively high, pulmonary embolism and bleeding events are rarer.
- No trials evaluated the following venous thromboembolism outcomes (symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis), and bleeding outcomes (surgical site bleeding, bleeding leading to infection).

Detailed Analysis

Study design and characteristics. Eighteen randomized controlled trials (N=1240) and two controlled observational studies (N=921) evaluated the overall baseline risk of venous

thromboembolism outcomes and bleeding outcomes in contemporary practice.[14,27-29,31,33,34,36,37,40,42-44,46,69,83,125,126,136,138] All eighteen randomized controlled trials were published as full text manuscripts. Twelve randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing total hip arthroplasty.[14,27,28,31,34,37,40,42,43,69,83,126] Five randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing total knee arthroplasty.[29,31,36,44,46] Two randomized controlled trials evaluated the overall baseline risk of venous thromboembolism or bleeding outcomes in patients undergoing hip fracture surgery. The earliest trial was published in 1980 while the most recent published in 2010.[36,46] The duration of followup ranged from the post-operative period to 2.4 years. Three trials received funding from industry,[31,46,126] five trials received funding from government and foundation,[27,42,43,69,83] one trial received funding from industry and government,[125] one trial received funding from government,[28] and in eight trials the funding source was not reported.[14,29,33,34,36,37,40,44]

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

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

Two controlled observational studies (N=921) evaluated the overall baseline risk of venous thromboembolism outcomes and bleeding outcomes in contemporary practice.[136,138] Both of these unfunded observational studies were published as full text manuscripts. One study was conducted in people undergoing total hip or total knee arthroscopy and those without chemical prophylaxis (N=136) all had contraindications to receive aspirin therapy which may not be representative of the natural course of embolization or bleeding.[136] It was not explicitly stated whether or not mechanical approaches could have been used in these patients. The second study was conducted in people undergoing total knee arthroplasty and those with no pharmacological or mechanical prophylaxis (n=785). Since they were derived mostly from orthopedic practices where a lack of prophylaxis is routine, it is not subject to the same confounds as the first observational study.[138]

Outcome evaluation. A summary of the baseline risk of venous thromboembolism and bleeding outcomes from included trials is presented in

Table 7 to Table 9. Five trials evaluated the occurrence of pulmonary embolism among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis (patients were randomly allocated to control or placebo).[14,27,28,42,43] In these trials, the pooled incidence of pulmonary embolism was 6 percent [0.06 (95 percent CI = 0.003 to 0.18)]. A high level of statistical heterogeneity was detected (I^2 = 88.8 percent), but publication bias was not found (Egger's P = 0.106). Only one trial evaluated the occurrence of fatal and nonfatal pulmonary embolism.[42] In this trial, 0 out of 50 patients (0 percent) developed fatal pulmonary embolism and 1 out of 50 patients (2 percent) developed nonfatal pulmonary embolism.

Two trials evaluated the occurrence of pulmonary embolism among patients undergoing total knee arthroplasty who received no pharmacologic or mechanical prophylaxis (patients were randomly allocated to control or placebo).[29,44] In these trials, the pooled incidence of pulmonary embolism was 1 percent [0.01 (95 percent CI = 0.0007 to 0.04)]. Out of these trials, one trial also evaluated the occurrence of fatal and nonfatal pulmonary embolism.[44] In this trial no patients developed fatal or nonfatal pulmonary embolism.

In hip fracture surgery, 2 of 63 patients (3 percent) who received no pharmacologic or mechanical prophylaxis developed pulmonary embolism in the only available trial.[125] Both of the pulmonary embolism events were nonfatal.

Eight trials evaluated the occurrence of deep vein thrombosis among patients who received no pharmacologic or mechanical prophylaxis undergoing total hip arthroplasty.[14,27,28,34,40,42,43,126] In these trials, the pooled incidence of deep vein thrombosis was 39 percent [0.39 (95 percent CI = 0.25 to 0.53)]. A high level of statistical heterogeneity was detected (I^2 = 85.6 percent), but publication bias was not found (Egger's P = 0.118). Four trials evaluated the occurrence of proximal deep vein thrombosis among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis.[14,27,42,126] In these trials, the pooled incidence of proximal deep vein thrombosis was 32 percent [0.32 (95 percent CI = 0.14 to 0.54)]. A high level of statistical heterogeneity and publication bias were detected (I^2 = 87.2 percent, Egger's P = 0.030). Two trials evaluated the occurrence of distal deep vein thrombosis among patients undergoing total hip arthroplasty who received no pharmacologic or mechanical prophylaxis.[14,27] In these trials, the pooled incidence of distal deep vein thrombosis was 30 percent [0.30 (95 percent CI = 0.04 to 0.68)]. In the trial by Kim and colleagues in 2003, the authors also determined the risk of deep vein thrombosis among patients who could have had more than one hip operated on. This data was not suitable for pooling but deep vein thrombosis, proximal deep vein thrombosis, and distal deep vein thrombosis occurred in 72 of 300 hips (24 percent), 42 of 300 hips (14 percent), and 52 of 300 hips (17.3 percent) operated on.[14]

Two trials evaluating the occurrence of deep vein thrombosis among patients undergoing total knee arthroplasty who received no pharmacologic or mechanical prophylaxis were suitable for pooling.[29,36] In these trials, the pooled incidence of deep vein thrombosis was 46 percent [0.46 (95 percent CI = 0.05 to 0.91)]. Two trials that were suitable for pooling evaluated the occurrence of proximal deep vein thrombosis among patients undergoing total knee arthroplasty who received no prophylaxis.[29,36] In these trials, the pooled incidence of proximal deep vein thrombosis was 17 percent [0.17 (95 percent CI = 0.01 to 0.66)]. The same two trials evaluated the occurrence of distal deep vein thrombosis among patients undergoing total knee arthroplasty who received no pharmacologic or mechanical prophylaxis.[29,36] In these trials, the pooled incidence of distal deep vein thrombosis was 22 percent [0.22 (95 percent CI = 0.12 to 0.35)]. In a trial not suitable for pooling, patients who had one or more total knee replacements had a deep

vein thrombosis, proximal deep vein thrombosis and distal deep vein thrombosis in 22 of 32 legs (68.8 percent), 6 of 32 legs (18.8 percent), and 13 of 32 legs (40.6 percent), respectively.[44]

One trial evaluated the occurrence of deep vein thrombosis among patients undergoing hip fracture surgery who received no pharmacologic or mechanical prophylaxis.[33] The pooled incidence of deep vein thrombosis could not be calculated because only one study was available. In this trial, 18 out of 38 patients (47 percent) undergoing hip fracture surgery developed deep vein thrombosis. No trials evaluated the occurrence of proximal or distal deep vein thrombosis among patients undergoing hip fracture surgery who received no pharmacologic or mechanical prophylaxis.

Five trials evaluated the occurrence of major bleeding among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis.[31,34,37,42,83] In these trials, the pooled incidence of major bleeding was 1 percent [0.01 (95 percent CI = 0.002 to 0.03)]. A low level of statistical heterogeneity was detected (I^2 = 22.0 percent), but the publication bias was not found (Egger's P = 0.085). Five trials evaluated the occurrence of minor bleeding among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis.[31,37,42,69,83] In these trials, the pooled incidence of minor bleeding was 6 percent [0.06 (95 percent CI = 0.01 to 0.16)]. A high level of statistical heterogeneity and publication bias were detected (I^2 = 90.0 percent, Egger's P = 0.023). In the two trials that evaluated the occurrence of major bleeding leading to reoperation among patients undergoing total hip arthroplasty who received either no prophylaxis or only mechanical prophylaxis, no events occurred.[37,69] In the one trial that evaluated bleeding leading to transfusion no events occurred.[69]

Two trials evaluated the occurrence of major bleeding among patients undergoing total knee arthroplasty who received either no prophylaxis or only mechanical prophylaxis.[31,46] In these two trials, the pooled incidence of major bleeding was 3 percent [0.03 (95 percent CI = 0.002 to 0.08)]. Two trials evaluated the occurrence of minor bleeding among patients undergoing total knee arthroplasty who received either no prophylaxis or only mechanical prophylaxis.[31,46] In these two trials, the pooled incidence of minor bleeding was 5 percent [0.05 (95 percent CI = 0.03 to 0.08)]. In the one trial that evaluated the occurrence of major bleeding leading to reoperation among patients undergoing total knee arthroplasty who received either no prophylaxis or only mechanical prophylaxis, no events occurred.[46] In the one trial that evaluated bleeding leading to transfusion no events occurred.[46]

One trial evaluated the occurrence of major bleeding among patients undergoing hip fracture surgery who received either no prophylaxis or only mechanical prophylaxis.[125] In this trial, 5 out of 63 patients (8 percent) undergoing hip fracture surgery developed major bleeding. No trials evaluated the occurrence of minor bleeding, major bleeding leading to reoperation or major bleeding leading to transfusion in this population.

In the first observational study, incidence of fatal pulmonary embolism, nonfatal pulmonary embolism, and deep venous thrombosis after total hip or total knee arthroplasty were 0 percent, 0 percent, and 1.5 percent, respectively.[136] However, these patients all had contraindications to aspirin prophylaxis and might not be representative of the overall population undergoing orthopedic surgery. It is also not clear whether or not mechanical prophylaxis was allowed. In the second observational study, there was no occurrence of deep vein thrombosis but 2 of 785 patients (0.3 percent) undergoing total knee arthroplasty developed pulmonary embolism, both episodes were nonfatal.[138]

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

Author, Year	PE	Fatal PE	Non fatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major bleeding leading to reoperation	Bleeding leading to transfusion
Kim, 2003[14]	0/200	---	---	20/100 (20%)	12/100 (12%)	14/100 (14%)	---	---	---	---
Kim, 1998[34]	---	---	---	10/50 (20%)	---	---	0/50 (0%)	---	---	---
Kalodiki, 1996[126]	---	---	---	13/14 (92.9%)	8/14 (57.1%)	---	---	---	---	---
Torholm, 1991[40]	---	---	---	16/54 (29.6%)	---	---	---	---	---	---
Alfaro, 1986[28]	1/30 (3.33%)	---	---	9/30 (30.0%)	---	---	---	---	---	---
Turpie, 1986[42]	1/50 (2.0%)	0/50 (0.0%)	1/50 (2.0%)	20/39 (51.3%)	9/39 (23.1%)	---	2/50 (4.0%)	0/50 (0.0%)	---	---
Welin-Berger, 1982[43]	1/20 (5.0%)	---	---	5/20 (25.0%)	---	---	---	---	---	---
Modig, 1981[27]	9/30 (30%)	---	---	16/30 (53.3%)	14/30 (46.67%)	15/30 (50.00%)	---	---	---	---
Fuji, 2008[31]	---	---	---	---	---	---	0/101 (0.0%)	2/101 (2.0%)	---	---
Samama, 1997[37]	---	---	---	---	---	---	1/75 (1.3%)	21/75 (28.0%)	0/75 (0.0%)	---
Francis, 1992[69]	---	---	---	---	---	---	---	4/98 (4.1%)	0/98 (0%)	0/98 (0%)
Paiement, 1987[83]	---	---	---	---	---	---	0/66 (0%)	3/66 (4.5%)	---	---

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism

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

Author, Year	PE	Fatal PE	Nonfatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major bleeding leading to reoperation	Bleeding leading to transfusion
Chin, 2009[29]	1/110 (0.9%)	---	---	24/110 (21.8%)	3/110 (2.7%)	21/110 (19.1%)	---	---	---	---
Wilson, 1992[44]	0/32 (0.0%)	0/32 (0.0%)	0/32 (0.0%)	22/32 (68.8%)*	6/32 (18.8%)*	13/32 (40.6%)*	---	---	---	---
McKenna, 1980[36]	---	---	---	9/12 (75.0%)	5/12 (41.7%)	4/12 (33.3%)	---	---	---	---
Fuji, 2010[46]	---	---	---	---	---	---	1/124 (0.8%)	6/124 (4.8%)	0/124 (0.0%)	0/124 (0.0%)
Fuji, 2008[31]	---	---	---	---	---	---	4/89 (4.5%)	4/89 (4.5%)	---	---

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

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism

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

Author, Year	PE	Fatal PE	Nonfatal PE	DVT	Proximal DVT	Distal DVT	Major Bleeding	Minor Bleeding	Major bleeding leading to reoperation	Bleeding leading to transfusion
Jorgensen, 1992[33]	---	---	---	18/38 (47.4%)	---	---	---	---	---	---
Powers, 1989[125]	2/63 (3.2%)	0/63 (0.0%)	2/63 (3.2%)	---	---	---	5/63 (7.9%)	---	---	---

Abbreviations: DVT=deep vein thrombosis; PE=pulmonary embolism

Key Question 2

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

Key Points

- Sixteen randomized controlled trials and four observational studies evaluated the impact of surgical characteristics on venous thromboembolic or bleeding outcomes.
    - The majority of literature compared general to regional anesthesia, with representation from all three major orthopedic surgeries. There was mixed effects on the risk of pulmonary embolism, deep vein thrombosis, asymptomatic, proximal and distal deep vein thrombosis although consistently showed no effect on the risk of symptomatic deep vein thrombosis and major bleeding while minor bleeding could not be evaluated because no events occurred. One trial compared spinal versus regional anesthesia although no deep vein thromboses occurred.
    - Cemented versus noncemented arthroplasty consistently showed no impact on pulmonary embolism, proximal and distal deep vein thrombosis and was mixed on the risk of deep vein thrombosis.
        - Bone vacuum cement versus standard procedure decreased the risk of deep vein thrombosis and proximal deep vein thrombosis while having no effect on distal deep vein thrombosis or major bleeding. Minor bleeding could not be evaluated because no events occurred.
    - Tourniquet use versus no use consistency showed no impact on the risk of asymptomatic or symptomatic deep vein thrombosis while distal deep vein thrombosis could not be evaluated because no events occurred. One trial compared early versus late tourniquet release on the risk of deep vein thrombosis although no events occurred.
    - Modified limb position consistently showed no impact on the risk of deep vein thrombosis or proximal deep vein thrombosis and the impact on pulmonary embolism could not be evaluated because no events occurred.
    - Tissue fibrin use versus no tissue fibrin showed no impact on fatal pulmonary embolism while the impact on deep vein thrombosis could not be evaluated because no events occurred.
    - Primary versus revision surgery influenced the odds of deep vein thrombosis (although magnitude and direction were not reported) while perioperative blood loss, operative time, and blood transfusions had no effect.
- Ten observational studies evaluated the impact of patient characteristics on venous thrombembolic outcomes all using multivariate regression analysis. No studies or trials evaluated the impact of patient characteristics on harms. Overall few patient characteristics were evaluated by more than one study for each outcome of interest.
    - The odds of symptomatic objectively confirmed venous thromboembolism was consistently increased by congestive heart failure, inactive malignancy, hormone replacement therapy, living at home, intertrochanteric or subtrochanteric fractures, increased hemoglobin on admission, personal or familial history of venous

thrombembolism, and varicose veins while those consistently showing no effect on the odds included age and male gender.

- The odds of pulmonary embolism were consistently increased by age and genitourinary tract infection, consistently decreased by cardiovascular disease, consistency unaffected by a history of phlebitis, phlebitis in the opposite extremity, thyroid hormone replacement therapy, history of pulmonary embolism, varicosity, or peripheral vascular disease.
- The odds of deep vein thrombosis were consistently uninfluenced by height, weight, Factor V Leiden mutation, and mixed effects were seen with age, obesity, and gender. Smoking was reported to have little to no effect although magnitude and direction of effect was not reported.
- The odds of symptomatic deep vein thrombosis were consistently increased by metabolic syndrome while were consistently unaffected by age, gender, education, diabetes mellitus, hypertension, hyperlipidemia, body mass index, and presence of comorbidities.
- The odds of proximal deep vein thrombosis were increased by congestive heart failure while were unaffected by age, prior deep vein thrombosis, inactive malignancy, current hormone replacement therapy, chronic tobacco use, and blood disorders (sickle-cell trait, polycthymia vera, and thrombocytopenia).

Detailed Analysis

Study design and characteristics. Sixteen randomized controlled trials (N=1777), six controlled observational studies (N=11215) and four nested observational studies (N=2469) evaluated the impact of patient, surgical, or postsurgical characteristics on the risk of venous thromboembolic or bleeding outcomes.[11-17,19,21-27,49,61,66,110,128-133,187] All sixteen randomized controlled trials evaluated surgical characteristics and were published as full text manuscripts. Six trials compared general to regional anesthesia,[13,17,23,25,27,187] one trial compared spinal to epidural anesthesia,[12] three trials evaluated cemented arthroplasty techniques,[14,15,19,61] three trials evaluated aspects of tourniquet use during surgery,[21,24,26] two trials evaluated limb positioning[11,22] and one trial evaluated tissue fibrin adhesive.[16] Six trial enrolled patients who had total hip replacement surgery (n=773),[11,14,15,19,27,187] nine trials enrolled patients who had total knee replacement surgery (n=964),[12,13,16,17,21-24,26] and one trial enrolled patients who had hip fracture surgery (n=40).[25] The earliest trial was published 1981 while the most recent in 2008. The duration of followup ranged from the post operative time period to one year. One trial was funded by industry,[19] two trials were funded by government/foundation,[15,23] two trials were funded by government/foundation and industry[13,27] two trials were unfunded,[16,26] seven trials did not disclose funding source,[11,12,14,17,21,24,25,187]

The mean age of patients ranged from 54.9 to 73 years. Females represented between 37.5 to 70.3 percent of the enrolled population. Mean weight ranged from 72.9 to 100 kilograms. History of venous thromboembolism ranged from zero percent to 10 percent. Other baseline characteristics were scarcely reported. Eight studies evaluated exclusively patients who had primary surgery. Mean hospital length of stay was reported in four trials and ranged from 10.4 to 12.7 days. Mean duration of surgery ranged from 51 to 161.3 minutes.

Ten controlled observational studies evaluated the impact of patient and surgical characteristics on the incidence of venous thromboembolic or bleeding outcomes. Four were nested in randomized controlled trials[49,61,66,110] while six were controlled observational

studies.[128-133] All four nested studies evaluated patients who had total hip replacement surgery (n=2469), one study evaluated patients who had total knee replacement surgery (n=1460), one study evaluated patients who had hip fracture surgery (n=5300), three studies evaluated patients who had either total knee or hip replacement surgery (n=2035) and one study evaluated all three major orthopedic surgeries (n=2420). The most recent study was published in 2009 while the earliest was published in 1991. Three studies did not report funding source,[129,131,132] two were funded by industry,[128,130] and one was funded by academia and foundation.[133]

The mean age of patients ranged from 62.3 to 80 years. Females represented between 50.0 to 82.91 percent of the enrolled population. Mean weight was rarely reported and ranged from 71 to 75 kilograms in two studies. Four studies evaluated exclusively patients who had primary surgery while two evaluated revision surgery as well. Mean hospital length of stay was reported in four studies and ranged from 4.2 to 10 days. Other baseline and procedural characteristics were scarcely reported.

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

Surgical characteristics

Anesthesia regimens. Seven randomized controlled trials and two observational studies evaluated the anesthesia regimen used during major orthopedic surgery. One of the randomized controlled trials compared spinal anesthesia to epidural anesthesia[12] while the other six trials and the two nested observational studies compared general anesthesia to regional anesthesia.[13,17,23,25,27,49,66,187]

One randomized controlled trial by Farag and colleagues compared spinal versus epidural anesthesia in 38 patients who had total hip replacement surgery.[12] All patients received bilateral antiembolism compression stockings while patients in the spinal anesthesia group also received prophylaxis with a low molecular weight heparin. Presence of deep vein thrombosis was assessed on days 3 and 10 postoperatively and there were no events at either time point.

Six randomized controlled trials compared general versus regional anesthesia in patients who had major orthopedic surgery.[13,17,23,25,27,187] Two trials did not provide patients with mechanical or pharmacologic venous thromboembolism prophylaxis.[25,27] The first of these trials by McKenzie and colleagues randomized 40 patients who had hip fracture surgery to receive general anesthesia or subarachnoid blockade. The incidence of deep vein thrombosis and of asymptomatic deep vein thrombosis was significantly higher in those who received general anesthesia as opposed to subarachnoid blockade (75 percent versus 40 percent, $p < 0.05$; 75 percent versus 25 percent, $p = 0.004$). No deep vein thromboses were symptomatic in the group that received general anesthesia while three symptomatic events occurred in the subarachnoid blockade group (0 percent versus15 percent, $p = 0.230$). The second of these trials by Modig and colleagues randomized 30 patients who had total hip replacement surgery to receive general anesthesia versus epidural anesthesia.[27] There was no significant difference in the incidence of pulmonary embolism in the general versus epidural anesthesia groups 14 days after surgery (46.7 percent versus 13.3 percent, $p = 0.111$). Although there was no significant difference in the incidence of deep vein thrombosis in the regional versus general anesthesia groups (33.3 percent

versus 73.3 percent, p = 0.067), significantly less patients had a proximal deep vein thrombosis defined as an isolated femoral or calf and femoral vein thrombosis (20 percent versus 73.3 percent, p <0.05) or a distal deep vein thrombosis defined as an isolated calf or calf and femoral vein thombosis (26.67 percent versus 73.3 percent, p = 0.028) in the regional versus general anesthesia group.

The remaining four trials that compared general to regional anesthesia allowed the use of mechanical or pharmacological prophylaxis for venous thromboembolism.[13,17,23,187] The first trial by Williams-Russo and colleagues randomized 262 patients who had total knee replacement surgery to receive general versus epidural anesthesia.[23] All patients received elastic stockings on postoperative day 1 as well as pharmacologic prophylaxis based on physician preference, which was aspirin 325mg twice daily in the majority of cases (71.8 percent). However, some patients received warfarin prophylaxis and the investigators reported outcomes only for those patients who received aspirin. There was no significant difference in the incidence of deep vein thrombosis in the general versus epidural anesthesia groups (48 percent versus 40 percent, p = 0.300). All deep vein thromboses were distal in location. The second trial by Mitchell and colleagues randomized 72 patients who had total knee replacement surgery to receive general versus epidural anesthesia.[17] Additionally, male patients received aspirin 650mg twice daily while female patients received low dose warfarin prophylaxis. Investigators reported there was no significant difference in gender between the two groups, with the majority of enrolled subjects being male (62.5 percent). There was no significant difference in the incidence of proximal deep vein thrombosis between the general and regional anesthesia groups (63 percent versus 46 percent, p = 0.256). The third trial by Jorgensen and colleagues randomized 48 patients who had total knee replacement surgery to general anesthesia versus epidural anesthesia.[13] All patients also wore graded compression stockings. Significantly fewer patients had a deep vein thrombosis in the epidural anesthesia group versus the general anesthesia group (17.6 percent versus 59.1 percent, p = 0.02). When comparing general versus epidural anesthesia, there was no significant difference in symptomatic deep vein thrombosis (9.1 percent versus 0 percent, p = 0.586), asymptomatic deep vein thrombosis (50 percent versus 17.6 percent , p = 0.080), proximal deep vein thrombosis (13.6 percent versus 5.9 percent, p = 0.795) or distal deep vein thrombosis (45.5 percent versus 11.8 percent, p = 0.056). A fourth trial by Planes and colleagues randomized 194 patients who had total hip replacement surgery to receive general anesthesia plus enoxaparin 40mg 12 hours prior to surgery, spinal anesthesia plus enoxaparin 20mg one hour after the onset of anesthesia, or spinal anesthesia with no immediate use of enoxaparin.[187] Patients in all three groups continued enoxparin 40mg 12 hours after surgery and then daily thereafter. This study was not found to be very useful to this review as the general anesthesia group received enoxaparin using a different regiment as one spinal anesthesia group and the other spinal anesthesia group received no enoxaparin at all. No patients had symptoms of a pulmonary embolism. There was no significant difference in the incidence of proximal deep vein thrombosis between the three groups, respectively (6.5 percent, 6.6 percent, 6 percent, p = 0.993). However, there was a significant difference in the incidence of distal deep vein thrombosis when comparing the three groups, respectively (0 percent, 5 percent, 11 percent, p = 0.007) and when comparing general anesthesia plus immediate enoxaparin versus epidural anesthesia without immediate enoxaparin (0 percent versus 11 percent, p = 0.013). Major bleeding was not significantly different between the three groups, respectively (3.2 percent, 1.6 percent, 1.5 percent, p = 0.764) and there were no episodes of minor bleeding.

Two nested observational studies evaluated the impact of general versus regional anesthesia on the incidence of deep vein thrombosis. The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.[66] The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a multivariate regression model. Authors report that general anesthesia versus regional anesthesia significantly influenced the risk of deep vein thrombosis although they did not report the magnitude or direction of the effect. The second study was nested in a randomized controlled trial which compared low-dose warfarin to intermittent pneumatic compression in patients who had total hip arthroplasty.[49] Multivariate regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that the type of anesthesia did not significantly influence the incidence of deep vein thrombosis.

Cemented arthroplasty. Three randomized controlled trials and three nested observational study evaluated aspects of cemented arthroplasty during total hip replacement surgery.[14,15,19,61] The first trial evaluated 200 patients who had unilateral or bilateral primary total hip replacement surgery and were randomized to undergo cemented versus cementless arthroplasty.[14] Patients who had bilateral surgery were randomized by knee, therefore outcomes were reported out of the number of knees operated on (n=300). No concurrent pharmacologic or mechanical prophylaxis was allowed. When comparing cemented versus cementless procedures, there was no significant difference in the rate of deep vein thrombosis (20.7 percent versus 27.3 percent, $p = 0.654$), proximal deep vein thrombosis (12.7 percent versus 15.3 percent, $p = 0.618$) or distal deep vein thrombosis (14.7 percent versus 20 percent, $p = 0.286$). The second trial evaluated 250 patients who had unilateral total hip replacement and randomized to receive cemented versus noncemented Mallory head prosthesis.[15] The majority of patients received prophylaxis with aspirin (46.4 to 58.9 percent) although some patients received warfarin (28.8 to 43.5 percent), both (8.2 to 10.1 percent), or neither (0.0 to 4.1 percent). When comparing cemented arthroplasty to cementless arthroplasty, there was no significant difference in the rate of pulmonary embolism (2.4 percent versus 0.8 percent, $p = 0.37$), deep vein thrombosis (50.0 percent versus 47.1 percent, $p = 0.73$), proximal deep vein thrombosis (3.0 percent versus 4.8 percent, $p = 0.67$) or distal deep vein thrombosis (50.0 percent versus 46.4 percent, $p = 0.67$).

The third trial evaluated 130 patients who had primary total hip replacement surgery and were randomized to undergo the surgical procedure with a bone vacuum cementing technique versus a standard cementing technique.[19] All patients also received prophylaxis with the low molecular weight heparin nadroparin and bilateral thigh-high antithromboembolic stockings. There were no clinically suspected pulmonary emboli in the groups compared during the 45 day followup. There was a significantly lower rate of deep vein thrombosis in the group that received bone vacuum cementing versus standard cementing (3 percent versus 18 percent, $p = 0.009$) as well as a significantly lower rate of proximal deep vein thrombosis (0 percent versus 11 percent, $p = 0.020$). There was no difference in the rate of distal deep vein thrombosis between the intervention and control groups (3 percent versus 8 percent, $p = 0.437$). This trial also evaluated major and minor bleeding. No major bleeding episodes occurred in the groups compared and the

rate of minor bleeding was not significantly different between the intervention and control groups (8 percent versus 6 percent, p =1.00).

Three nested observational studies evaluated the impact of cemented prosthesis on the risk of deep vein thrombosis. The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to unfractionated heparin in patients who had total hip replacement surgery.[61] In the patients who received desirudin therapy, risk factors associated with the development of deep vein thrombosis were analyzed with multiple regression analysis and adjusted for peak partial thromboplastin time, age, gender, obesity, smoking habits and cemented surgery. Authors reported that cemented prosthesis had little to no influence on the risk of deep vein thrombosis although the magnitude or direction of effect was not reported. The second study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.[66] The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a multiple regression model. The authors reported that cemented versus noncemented prosthesis significantly influenced the risk of deep vein thrombosis ($p < 0.02$) although the magnitude and direction of the effect were not reported. The third study was nested in a randomized controlled trial which compared low-dose warfarin to intermittent pneumatic compression in patients who had total hip arthroplasty.[49] Multiple regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that the type of stem did not influence the incidence of deep vein thrombosis.

Tourniquet use. Three randomized controlled trials evaluated aspects of tourniquet use during total knee replacement surgery.[21,24,26] The first trial evaluated 80 patients who had primary, cemented total knee replacement surgery and were randomized to have a pneumatic tourniquet placed around the thigh and inflated versus a pneumatic tourniquet placed around the thigh but not inflated.[24] All patients received prophylaxis with dalteparin as well. Four symptomatic deep vein thromboses, all femoral in location, occurred 8 to 21 days postoperatively in the group whose tourniquet was inflated while none occurred in the control group (10 percent versus 0 percent, p= 0.116) although the difference was not significant. No distal deep vein thromboses occurred in the groups compared. In a second trial, 77 patients who also underwent cemented total knee replacement surgery were randomized to undergo surgery with an inflated tourniquet versus no tourniquet use.[26] One asymptomatic deep vein thrombosis in the popliteal vein was diagnosed during the postoperative ultrasound on day 10 in a patient who had surgery with the use of a tourniquet while none occurred in the control group (2.7 percent versus 0 percent, p = 0.481) and this finding was not significant. No distal deep vein thrombosis occurred in the groups compared.

The third trial evaluated 20 patients who had bilateral cemented total knee replacement surgery with the use of a tourniquet. Within a patient, each knee was randomized to be operated on with tourniquet release and hemostasis prior to wound closure versus tourniquet release after wound closure and pressure dressing.[21] All patients also received low molecular weight heparin prophylaxis with nadroparin. No deep vein thromboses occurred in the groups compared.

Limb positioning. Two randomized controlled trials evaluated variations of limb position during major orthopedic surgery.[11,22] The first trial evaluated 118 patients who had primary, cemented total knee replacement and were randomized to two groups.[22] The intervention group underwent the surgical procedure with a time limit for flexion and dislocation of the knee in order to minimize the total time the knee was in extreme flexion. The control group underwent the surgical procedure with the knee maintained in flexion and dislocation for the duration of the surgery. All patients received aspirin postoperatively for venous thromboembolism prophylaxis and the outcomes were reported out of the number of knees operated on. There was no significant difference in the rate of deep vein thrombosis between the intervention and control group (38 percent versus 42 percent, $p = 0.60$) or in the rate of proximal deep vein thrombosis between the intervention and control groups (16 percent versus 12 percent, $p = 0.40$).

The second trial evaluated 160 patients who had primary, cemented total hip replacement surgery and were randomized into two groups.[11] The intervention group underwent the surgical procedure in a modified position to maintain femoral blood flow monitored with ultrasound whereas the control group underwent the surgical procedure without femoral blood flow monitoring in a full figure-of-four positioning of the leg. All patients received prophylaxis with the low molecular weight heparin nadroparin and customized anti-thrombosis stockings. No clinically suspected pulmonary emboli occurred in the groups compared. There was no significant difference in the rate of symptomatic deep vein thrombosis between the intervention and control groups (0 percent versus 4 percent, $p > 0.05$). All deep vein thrombosis occurred in patients who were in the control group, one of which was femoral, one in the lower leg, and one patient had involvement of the popliteal vein and lower leg.

Tissue fibrin adhesive. One randomized controlled trial evaluated 58 patients who had unilateral, cemented, total knee replacement surgery and randomized patients to receive treatment with tissue fibrin adhesive (Octacol F15) versus standard methods of hemostasis.[16] All patients received enoxaparin 40mg subcutaneously every 12 hours prior to surgery and then every 12 hours after surgery. This trial did not report any bleeding outcomes of interest. No patients developed an ultrasound confirmed deep vein thrombosis and one patient in the control group suffered from a fatal pulmonary embolism while none occurred in the group that received tissue fibrin adhesive (3.5 percent versus 0 percent, $p =1.00$).

Primary or revision surgery, perioperative blood loss, operative time, and blood transfusions. One nested observational study evaluated the impact of additional surgical characteristics on their impact on the incidence of deep vein thrombosis. This study was nested in a randomized controlled trial which compared low-dose warfarin to intermittent pneumatic compression in patients who had total hip arthroplasty.[49] Multiple regression analysis was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that revision versus primary surgery significantly influenced the incidence of deep vein thrombosis although perioperative blood loss, operative time, and blood transfusions did not.

Patient characteristics

Symptomatic objectively confirmed venous thromboembolism. Three controlled observational studies evaluated the impact of patient specific characteristics on the incidence of symptomatic objectively confirmed venous thromboembolism.[128,130,132] The first study by Dorr and colleagues evaluated patients who had total hip or knee replacement surgery and compared patients who were considered high risk to those considered low risk to evaluate the incidence of thromboembolism.[128] Low risk was defined as having none or at least one of the following: congestive heart failure, prior deep vein thrombosis more than 5 years ago, inactive malignant disease, current use of hormone replacement therapy, chronic tobacco use, blood disorders of the sickle-cell trait, polycythemia vera or thrombocytopenia. Within the low risk group, multivariate analysis of the risk factors for symptomatic objectively confirmed venous thromboembolism, adjusted for age was conducted. Congestive heart failure [adjusted odds ratio (AOR) 7.7, p = 0.0001), inactive malignant disease (AOR 3.1, p = 0.014), and hormone replacement therapy (AOR 3.2, p = 0.008) increased the odds of symptomatic objectively confirmed venous thromboembolism. Authors reported that age was not a significant risk factor in the analysis. The second study by McNamara and colleagues evaluated patients who had hip fracture surgery and compared patients with and without symptomatic objectively confirmed venous thromboembolism to assess for risk factors.[132] Multivariate analysis adjusted for age, gender, residence on admission (own home versus institution), mean hemoglobin on admission and type of fracture (intracapsular, intertrochanteris, subtrochanteric) showed that patients who lived in their own home [AOR 2.24 (1.32 to 3.82), p=0.003], those who presented with intertrochanteric fractures [AOR 2.15 (1.46 to 3.17), p = 0.001] or subtrochanteric fractures [AOR 1.51 (0.53 to 4.30), p = 0.001], or those with elevated hemoglobin on admission [AOR 1.01 (1.0 to 1.03, p = 0.01] had an increased odds of symptomatic objectively confirmed venous thromboembolism. Male gender [AOR 0.64 (0.38 to 1.07), p = 0.09] and age [AOR 1.0 (0.98 to 1.02), p = 0.9] did not significantly impact the risk of symptomatic objectively confirmed venous thromboembolism. The third study by Liezorovicz and colleagues evaluated Asian patients who had total hip or knee replacement surgery or hip fracture surgery and compared patients with or without the primary outcome to evaluate for risk factors.[130] The primary outcome was symptomatic objectively confirmed venous thromboembolism or sudden death at hospital discharge. Upon multivariate analysis adjusted for age, personal or familial history of venous thromboembolism, history of cancer or active cancer, varicose veins and chronic heart failure, personal or familial history of venous thromboembolism [AOR 26.9 (2.9 to 250.1)], chronic heart failure [AOR 5.1 (1.5 to 17.8)] and varicose veins [AOR3.6 (1.2 to 10.6)] were significant independent risk factors for the primary outcome. At the 1 month followup, personal or familial history of venous thromboembolism [AOR 18.1 (2.0 to 167.0)] and chronic heart failure [AOR 6.3 (2.1 to 18.6)] remained significant predictors of the primary outcome.

Pulmonary embolism. One nested case-controlled observational study evaluated the impact of patient specific characteristics on the incidence of pulmonary embolism.[131] This study by Lemos and colleagues evaluated patients who received warfarin prophylaxis as part of a larger trial and underwent total knee or hip replacement surgery. Patients with pulmonary embolism were compared to gender and procedure-matched controls without pulmonary embolism to determine risk factors for pulmonary embolism. Upon multivariate analysis, factors that increased the risk of pulmonary embolism included advancing age (p = 0.008) and genitourinary

infection ($p = 0.017$) while the presence of cardiovascular disease decreased the risk of pulmonary embolism ($p = 0.011$). History of phlebitis, use of thyroid replacement medication, history of pulmonary embolism, varicosities, phlebitis in the opposite extremity, or peripheral vascular disease were not found to be significant factors.

Deep vein thrombosis. Four observational studies evaluated the impact of patient characteristics on the incidence of deep vein thrombosis.[49,61,66,133] Three studies were nested within randomized controlled trials which compared different pharmacologic prophylaxis regimens.[49,61,66] The first study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to the low molecular weight heparin enoxaparin in patients who underwent total hip replacement surgery.[66] The influence of age, gender, type of anesthesia (general versus regional), type of prosthesis (cemented versus noncemented) and presence of obesity on the incidence of deep vein thrombosis were evaluated in a logistic regression model. The patient characteristics significantly influenced the risk of deep vein thrombosis, including age ($p < 0.001$) and presence of obesity ($p < 0.01$). The second study was nested in a randomized controlled trial comparing the direct thrombin inhibitor desirudin to unfractionated heparin in patients who had total hip replacement surgery.[61] In the patients who received desirudin therapy, risk factors associated with the development of deep vein thrombosis were analyzed with multiple regression analysis and adjusted for peak partial thromboplastin time, age, gender, obesity, smoking habits and cemented surgery. Patients over the age of 65 and females were at increased risk of deep vein thrombosis ($p < 0.01$ for each) and obesity was not a significant risk factor ($p > 0.2$). Authors also reported that smoking had little to no influence on the risk of deep vein thrombosis. The third study was nested in a randomized controlled trial which compared low-dose warfarin to intermittent pneumatic compression in patients who had total hip arthroplasty.[49] Logistic regression was used to evaluate the influence of age, gender, prophylactic regimen (warfarin versus intermittent pneumatic compression), perioperative blood loss, revision or primary surgery, height, weight, operative time, blood transfusions, type of anesthesia (general versus regional) and type of stem (cemented versus noncemented) on the incidence of deep vein thrombosis. The authors reported that aside from the treatment regimen, none of the patient characteristics (age, gender, height, and weight) significantly influenced the incidence of deep vein thrombosis.

One controlled observational study evaluated the impact of the factor V Leiden mutation on the incidence of deep vein thrombosis.[133] Logistic regression analysis adjusted for the presence of factor V Leiden mutation, surgical site, anticoagulant prophylaxis, and medical center. This study showed that factor V Leiden mutation did not significantly contribute to the risk of deep vein thrombosis.

Proximal deep vein thrombosis. Two controlled observational studies evaluated the impact of patient specific characteristics on the incidence of proximal deep vein thrombosis.[110,128] The first study by Dorr and colleagues evaluated patients who had total hip or knee replacement surgery and compared patients who were considered high risk to those considered low risk to evaluate the incidence of thromboembolism.[128] Low risk was defined as having none or at least one of the following: congestive heart failure, prior deep vein thrombosis more than 5 years ago, inactive malignant disease, current use of hormone replacement therapy, chronic tobacco use, blood disorders of the sickle-cell trait, polycythemia vera, or thrombocytopenia. Within the low risk group, multivariate analysis of the risk factors for proximal deep vein thrombosis, adjusted

for age and the listed risk factors was conducted. Only the presence of congestive heart failure (AOR 6.2, p = 0.0005) increased the odds of proximal deep vein thrombosis. The second study was nested in a randomized controlled trial which compared intermittent pneumatic compression alone or in combination with aspirin or warfarin in patients who had total hip replacement surgery.[110] Authors report that upon multiple regression analysis for the presence of proximal deep vein thrombosis adjusted for age, history of deep vein thrombosis, or revision surgery that age was a significant risk factor although the magnitude and direction of effect were not reported.

Symptomatic deep vein thrombosis. One controlled observational study evaluated patients who had total knee replacement to determine if the presence of metabolic syndrome impacted the incidence of symptomatic deep vein thrombosis.[129] Multivariate analysis adjusted for age, gender, education, body mass index, Charlson index, diabetes, hypertension, hypercholesterolemia, and metabolic syndrome showed that metabolic syndrome increased the odds of symptomatic deep vein thrombosis [AOR 3.0 (1.1 to 12.4)]. Age [AOR 0.9 (0.87 to 1.0)], gender [AOR 3.4 (0.4 to 18.5)], education [AOR 4.1 (0.8 to 20.6)], diabetes [AOR 3.1 (0.4 to 21.9)], hypertension [AOR 2.3 (0.6 to 32.2)], hypercholesterolemia [AOR 1.6 (0.2 to 33.5)], body mass index [AOR 1.1 (0.9 to 1.3)], and comorbidity [AOR 1.3 (0.9 to 2.2)] did not significantly impact the odds of proximal deep vein thrombosis.

Key Question 3

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

Key Points

- There was no reliable data concerning the relationship between final health outcomes other than pulmonary embolism and the occurrence of deep venous thrombosis.
- No trials or studies were available assessing whether deep venous thrombosis was correlated with or a multivariate predictor of pulmonary embolism.
- In the available studies, the routine use of prophylaxis reduced the occurrence rate of deep venous thrombosis and the scheduled anticoagulant treatment for deep venous thrombosis once it was detected may have diminished the number that developed into pulmonary embolism.
- In one observational study in total knee replacement surgery, the overall occurrence of pulmonary embolism and the subset with symptomatic pulmonary embolism occurred more frequently in those with deep venous thromboses. However the data was not adjusted for confounders and we could not discern whether these things are correlated or collinear.
- The available clinical trials were not very informative in determining the association between deep venous thrombosis and pulmonary embolism.

Detailed Analysis

Study design and characteristics. Eight randomized controlled trials (N=2114) and two controlled observational studies (N=2299) evaluated the relationship between surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) and patient important outcomes in patients undergoing major orthopedic surgery.[13,78,103,107,108,110,125,127,134,135] All eight randomized controlled trials were published as full text manuscripts. The first trial compared injectable low molecular weight heparin to combination of injectable low molecular weight heparin and mechanical prophylaxis.[107] The second trial compared injectable low molecular weight heparin agents to oral vitamin K antagonists.[78] The third trial compared oral antiplatelet agents to a combination of oral antiplatelet agents and mechanical prophylaxis.[108] The fourth trial reported comparisons between injectable unfractionated heparin, mechanical prophylaxis and combination of both these modalities.[127] The fifth trial compared mechanical prophylaxis to a combination of mechanical and oral vitamin K antagonists.[110] The sixth trial reported comparisons between oral vitamin K antagonists, oral antiplatelet agents and placebo.[125] The seventh trial compared two intermittent pneumatic compression devices.[103] The eight trial compared general to epidural anesthesia.[13] Three trials enrolled patients who had total hip replacement surgery (N = 502),[108,110,127] three trials enrolled patients who had total knee replacement surgery (N = 1141),[13,78,103] one trial enrolled patients with either total hip replacement or total knee replacement surgery,[107] and one trial enrolled patients who had hip fracture surgery (N = 194).[125] The earliest trial was published in 1989[125] and the most recent trial was published in 2008.[107] The duration of followup ranged from postoperative period to 180 days. Four trials received funding from the industry,[13,78,103,107] one trial received funding from industry and government,[125] two trials were unfunded[108,110] and in one trial funding source was not reported.[127]

The mean age of enrolled patients ranged from 62.3 years to 76.6 years. Females represented between 50.0 and 81.0 percent of the enrolled populations. The mean weight ranged from 71.0 to 88.0 kilograms. Few patients enrolled had a history of venous thromboembolism ranging from 0.0 to 14.0 percent. Two trials reported presence of varicosity ranging from 7.0 to 14.0 percent. One trial reported the percent of patients with a history of malignancy ranging from 15.6 to 18.6 percent.

Sixty eight to 100 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 0.0 to 89.2 percent. Mean duration of surgery ranged from 86.0 to 126.2 minutes and the mean duration of anesthesia was not reported. One trial directly compared general to epidural anesthesia. Otherwise, the use of general anesthesia was reported by two trials and ranged from 12.0 to 20.0 percent of patients. Two trials reported regional anesthesia use which ranged from 80.0 to 100.0 percent of patients. One trial reported combination of general and regional anesthesia ranging from 0.46 to 0.49 percent. The mean length of hospital stay was reported by two trials ranging from 3 to 10 days.

Of the two controlled observational studies one study (N=1257), published in 1992, compared patients who had total knee arthroplasty with and without calf thrombi to compare the risk of pulmonary embolism.[134] The second study (N=1042), published in 1997, evaluated patients who had total hip replacement surgery for the development of pulmonary embolism before and after discharge along with complications of low-dose warfarin use. One study did not report the funding source[134] while the other study reported being unfunded.[135]

Baseline and procedural characteristics of the patients enrolled in these studies were scarcely reported. One study reported the average age of patients was 59 years, 61.87 percent of the

surgeries were primary, 2.13 percent of patients had a history of venous thromboembolism and the average duration of hospitalization was 11 days.[135] The other study did not report specific baseline or procedural characteristics.[134]

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

Total Knee Arthroplasty.The most compelling evaluation of the link between deep venous thrombosis and pulmonary embolism was an observational study of 1257 patients (having 1625 total knee arthroplasty surgeries) undergoing total knee arthroplasty surgery at one hospital in the United States between 1974 and 1986.[134] Patients in this study had preoperative and postoperative perfusion lung scans and postoperative venograms per standard hospital practice. There were positive lung scans for pulmonary embolism (symptomatic and asymptomatic) in 6.9 percent of patients with calf thrombi versus 2.0 percent of patients without calf thrombi ($p<0.001$). Symptomatic pulmonary embolism occurred in 1.6 percent of patients with calf thrombi versus 0.2 percent of patients with negative venograms ($p=0.034$). When patients with proximal thrombi were compared against those with no thrombi, 4.8 percent versus 2.0 percent (p=NS) had pulmonary embolism and 1.9 percent versus 0.2 percent (p=NS) had symptomatic pulmonary embolism.

Four trials evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after undergoing total knee arthroplasty. In the first trial, 417 patients undergoing total knee arthroplasty received either warfarin or enoxaparin prophylaxis.[78] Venography was done on postoperative day 14 or earlier if the patient was to be discharged or had suspected deep venous thrombosis via ultrasonography or impedance plethysmography. Overall, 185 patients developed deep venous thromboses of which 46 were proximal. Four patients developed pulmonary embolism with the three of the patients not having venography and one of these patients having a normal ultrasonography evaluation. The fourth patient had bilateral deep venous thromboses in both calves. In the second trial, 153 patients had total knee arthroplasty and received a low molecular weight heparin with or without a leg mechanical compression device.[107] Patients received a duplex ultrasound of the legs before discharge and were followed up for 3 months for signs and symptoms of pulmonary embolism. From this group, 19 had deep venous thrombosis (12.4 percent) of which one had developed a distal deep venous thrombosis detected by ultrasound at discharge and subsequently developed a pulmonary embolism 29 days later. Another patient with a negative ultrasound for deep venous thrombosis developed pulmonary embolism on postoperative day 2. In the third trial, 423 patients undergoing total knee arthroplasty received one of two pneumatic compression devices for prophylaxis.[103] Ultrasonography of the calf and thigh was performed 3-5 days after the operation and when symptoms of deep venous thrombosis were detected. Spiral computed tomography was used to detect pulmonary embolism in symptomatic patients. In this trial, 52 of 423 patients (12.3 percent) had deep venous thrombosis of which one patient (0.2 percent) developed pulmonary embolism. In this patient, the routine ultrasonography on the fourth postoperative day was negative for thrombi but a repeat test on day twelve was positive. No other pulmonary emboli occurred during the trial. In the fourth trial, 48 patients who had primary or revision knee arthroplasty were randomized to receive either general or epidural anesthesia. No pharmacologic

prophylaxis was administered but all patients wore thigh-length compression stockings.[13] All patients were screened on day 9-11 for deep vein thrombosis with bilateral ascending venography. A total of 16 patients developed a deep vein thrombosis, 13 in the general anesthesia group and three in the epidural anesthesia group. One patient with deep vein thrombosis confined to the lower leg in the general anesthesia group developed a nonfatal pulmonary embolism (confirmed with ventilation-perfusion scan) on postoperative day five.

Total Hip Arthroplasty. An observational study of 1042 patients (1244 hips) was conducted at a single medical center in the United States between 1987 and 1993.[135] All patients received prophylaxis with low dose warfarin (goal prothrombin time between 14 and 17 seconds). Followup continued for three months in this study but they did not define the monitoring schedule to determine the occurrence of pulmonary embolism or deep venous thrombosis. It appears that the investigators only scanned for deep venous thrombosis of pulmonary embolism when the patients had symptomatic complaints. Five total hip arthroplasties were followed by the development of symptomatic deep venous thrombosis (0.5 percent of hips). Four were proximal deep venous thromboses and one was distal, as confirmed by venography or ultrasonography. Three of the five hips (60 percent) with deep venous thrombosis occurred in patients who concurrently or subsequently developed pulmonary embolism. Overall, 12 total hip arthroplasties, including the three described above, resulted in symptomatic pulmonary embolism and 10 of 12 were diagnosed with a ventilation perfusion scan.

Four trials evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after total hip arthroplasty. In the first trial, 30 patients undergoing hip replacement surgery did not receive pharmacologic or mechanical prophylaxis but were randomized to receive general versus epidural anesthesia.[27] Bilateral venography was conducted 14 days prior to and after surgery in all patients as was perfusion lung scanning and chest radiography. A total of 16 patients (53.3 percent) developed a deep vein thrombosis, 11 in the general anesthesia group (36.7 percent) and five in the epidural anesthesia group (33.3 percent). Nine of the patients with a deep vein thrombosis (56.3 percent) were diagnosed with a pulmonary embolism [seven in the general anesthesia group (63.6 percent) and two in the epidural anesthesia group (40 percent)]. In the second trial 231 patients had total hip arthroplasty (a total of 250 hips) and received aspirin with or without a pneumatic compression boot.[108] Patients received venography of the thigh or calf on the sixth, seventh, or eighth postoperative days. One proximal thrombi (popliteal vein), 15 distal thrombi, and two pulmonary emboli occurred. The patients with pulmonary emboli had negative venograms before discharge but late pulmonary embolism approximately 3 weeks postoperatively. In the third trial, 75 patients undergoing total hip arthroplasty received heparin with aspirin, pneumatic pump compression, or both strategies.[127] Duplex ultrasonaography was conducted at baseline, 1 and 2 weeks after surgery with venograms confirming positive results. Five of the patients developed deep venous thrombosis, three patients were symptomatic, two were asymptomatic, and one developed pulmonary embolism. No pulmonary embolism was found aside for the patient with deep venous thrombosis. In the fourth trial, 212 patients (217 hips) undergoing total hip arthroplasty received pneumatic compression alone, with aspirin, or with warfarin.[110] Venography, ultrasonography, or both were conducted just before the patient was about to be discharged (4 to 13 days postoperatively). Twenty-two of the 217 arthroplasties (10.1 percent) resulted in deep venous thrombosis. The only pulmonary embolism occurred in a patient who also had a deep venous thrombosis detected by ultrasonography of the thigh.

Hip Fracture Surgery. One trial evaluated the occurrence of pulmonary embolism among patients with deep venous thrombosis after hip fracture surgery. In one trial, 194 patients undergoing hip fracture surgery received warfarin, aspirin, or placebo.[125] Patients had venography on day 21 or at the time of discharge. Venography was performed sooner if an iodine fibrinogen leg scan or impedance plethysmography was found to be positive. Sixty nine patients developed deep venous thrombosis or pulmonary embolism. Of the three patients with pulmonary embolism, one patient developed a deep venous thrombosis on postoperative day 10, was not treated with heparin but discharged and died of autopsy reported pulmonary embolism on day 20. Another patient had a positive impedance plethysmography test and pulmonary embolism on day 14 but the venogram was said to be inadequate while the final patient had a pulmonary embolism on day seven with a calf vein thrombus found in the left leg on day 10.

Key Question 4

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

Key Points

Pharmacologic Prophylaxis

- There is a moderate level of evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases the occurrence of deep vein thrombosis, proximal deep vein thrombosis, and distal deep vein thrombosis while significantly increasing minor bleeding.
    - The analyses of deep vein thrombosis have higher levels of heterogeneity, this is likely due in part, to the inclusion of trials evaluating multiple classes of pharmacologic therapy within the analysis and the inclusion of trials that were published prior to 2001 within the analysis.
- There is a low level of evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major venous thromboembolism and asymptomatic deep vein thrombosis.
- Pharmacologic prophylaxis did not significantly impact pulmonary embolism in the base case analysis but did significantly reduce the risk of pulmonary embolism in the trials not allowing any background prophylaxis in both groups.

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

Mechanical Prophylaxis

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

Detailed Analysis

Study design and characteristics. Nineteen randomized controlled trials (N=2613) and two controlled observational studies (N=5929) evaluated the impact of combined pharmacologic and mechanical modalities versus no thromboprophylaxis on final health, intermediate and adverse outcomes.[28-31,33-38,40,42-46,125,126,136,138] All nineteen randomized controlled trials were published as full text manuscripts. One full text manuscript included two independent randomized controlled trials.[31] Seventeen randomized controlled trials compared pharmacologic prophylaxis to no prophylaxis, [28,29,31,33-38,40,42,43,45,46,125,126] and of these 11 compared pharmacologic prophylaxis to a truly no prophylaxis.[28,29,33,36,40,42-44,125,126] Two randomized controlled trials compared

mechanical prophylaxis to no prophylaxis[30,44] and of these one compared mechanical prophylaxis to truly no prophylaxis.[44] To qualify as being "truly no prophylaxis" the trials had to compare pharmacologic or mechanical prophylaxis to placebo or no prophylaxis without the use of any concurrent prophylaxis in the groups compared; whereas in the broader category of studies comparing pharmacologic or mechanical prophylaxis versus placebo or no prophylaxis along with concurrent use of graduated compression stockings in the groups compared were also included. Thirteen trials exclusively enrolled patients who had total hip replacement surgery (N=1814),[28,30,31,34,35,37,38,40,42,43,45,46,126] four trials enrolled patients who had total knee replacement surgery (N=537),[29,31,36,44] and two trials enrolled patients who had hip fracture surgery (N=262).[33,125] The earliest trial was published in 1980 while the most recent published in 2010.[36,46] The duration of followup ranged from the postoperative period to 90 days. Four trials received funding from industry,[31,46,126] two trials received funding from government and foundation,[42,43] one trial received funding from industry and government,[125] two trials received funding from government,[28,45] one trial did not receive funding from any commercial party,[30] and in eight trials the funding source was not reported.[29,33-35,37,38,40,44]

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

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

Two controlled observational studies (N=5929) evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery.[136,138] Both studies were published as full text manuscripts. Both studies compared patients who received warfarin versus no prophylaxis while one study also compared patients who received aspirin versus no prophylaxis.[136] One study reported the outcomes separately for total hip replacement (N=2203) and then for total knee replacement (N=2050).[136] The second trial was limited to total knee replacement (N=1742).[138] No studies evaluated patients who had hip fracture surgery. The studies were published in 2009 and 2003, respectively. The duration of followup for both studies was 90 days. One trial was unfunded[138] while the other did not disclose the funding source.[136]

The mean age of patients ranged from 68 to 71 years. Other baseline characteristics were not reported in these studies. All patients underwent primary surgery. One study reported the surgical approach. For patients who had total hip replacement, the posterior approach was used while for the patients who had total knee replacement the medial parapatellar approach was used.[136] Other procedural characteristics as well as the mean hospital length of stay were not reported in these two studies.

Outcome evaluations. A summary of the results for key question 4 is presented in

Table 10**.**

Symptomatic objectively confirmed venous thromboembolism

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

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

Major venous thromboembolism

Pharmacologic prophylaxis versus no prophylaxis. One randomized controlled trial by Fuji and colleagues in 2010 evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major venous thromboembolism in patients who had major orthopedic surgery.[46] This trial evaluated patients who had total knee replacement and included two separate comparisons of an oral direct thrombin inhibitor; dabigatran 150mg (mg) daily and dabigatran 220mg daily versus placebo. The use of concurrent elastic stockings was allowed therefore this trial was not considered a trial comparing pharmacologic prophylaxis versus truly no prophylaxis. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major venous thromboembolism was significantly decreased [relative risk (RR) 0.21 (0.05 to 0.95), number needed to treat (NNT) 19 to 22] (Appendix Figure 1). Statistical heterogeneity and publication bias could not be calculated because there were too few comparisons.

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

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

Pulmonary embolism

Pharmacologic prophylaxis versus no prophylaxis. Eleven randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[28,29,31,35,37,42,43,45,46,125] The three trials by Fuji and colleagues each included two separate comparisons, as did the trials by Powers and Alfaro and colleagues.[28,31,46,125] The trial by Fuji and colleagues in 2010 and the trial by Samama and colleagues were excluded from the analysis because no events occurred in either group, as was one comparison from one of the trials by Fuji and colleagues in 2008. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of pulmonary embolism were not significantly different [(Peto's odds ratio) OR 0.38 (0.13 to 1.07)] (Appendix Figure 2).

Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.063).

When limiting the original analysis to trials that compared pharmacologic prophylaxis to truly no prophylaxis, five trials remained with the trials by Alfaro and Powers and colleagues each including two separate comparisons.[28,29,42,43,125] In patients who received pharmacologic prophylaxis versus truly no prophylaxis the risk of pulmonary embolism was significantly decreased [RR 0.30 (0.09 to 0.99), NNT 20] (Appendix Figure 3). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to trials published from 2001 to present; four trials remained, with the three trials by Fuji and colleagues each including two separate comparisons.[29,31,46] One trial by Fuji and colleagues and one comparison from a second trial by Fuji and colleagues was excluded from the analysis because no events occurred in the groups compared.[31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of pulmonary embolism were not significantly different [OR 0.40 (0.04 to 3.68)] (Appendix Figure 4). A higher level of statistical heterogeneity was detected (I^2 = 73.8 percent). When limiting the original analysis to total hip replacement surgery, seven trials remained, with the trials by Fuji and Alfaro and colleagues each including two separate comparisons.[28,31,35,37,42,43,45] The trial by Samama and colleagues and one comparison from the trial by Fuji and colleagues were excluded from the analysis because no events occurred in either groups compared.[31,37] In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of pulmonary embolism were not significantly different [OR 0.44 (0.12 to 1.66)] (Appendix Figure 5). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery, three trials remained, with the two trials by Fuji and colleagues each including two separate comparisons.[29,31,46] One trial by Fuji and colleagues was excluded form the analysis because no events occurred in either group compared.[46] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.31 (0.03 to 3.23)] (Appendix Figure 6). No statistical heterogeneity was detected (I^2 = 0 percent). When limiting the original analysis to hip fracture surgery, one trial by Powers and colleagues remained, with two separate comparisons.[125] In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of pulmonary embolism was not significantly different [RR 0.30 (0.04 to 2.42)] (Appendix Figure 7). Statistical heterogeneity could not be calculated because of too few studies.

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

Oral antiplatelet agents versus no prophylaxis. Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery with the trial by Alfaro and colleagues including two separate comparisons.[28,125] In patients who received oral antiplatelet agents versus no prophylaxis the risk of pulmonary embolism was not significantly different [RR 0.35 (0.07 to 1.87)] (Appendix Figure 8). Statistical heterogeneity was not detected (I^2 = 0 percent) and Egger's p-value could not be calculated due to the few number of studies.

Injectable low molecular weight heparins versus no prophylaxis. Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery with the two trials by Fuji and colleagues each contributing two separate comparisons.[29,31,35,37,42] One trial by

Samama and colleagues and one comparison from a trial by Fuji and colleagues were excluded from this analysis because no events occurred in either group compared.[31,37] In patients who received injectable low molecular weight heparin versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.55 (0.16 to 1.94)] (Appendix Figure 9). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.446).

Injectable unfractionated heparins versus no prophylaxis. One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[43] In this trial, patients who had total hip replacement surgery received either unfractionated heparin or no prophylaxis and the risk of pulmonary embolism was not significantly different [RR 0.33 (0.03 to 3.84)].

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[46] This trial evaluated patients who had total knee replacement and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral vitamin K antagonists versus no prophylaxis. One comparison from the trial by Powers and colleagues evaluated the impact of vitamin K antagonists versus no prophylaxis in patients who had major orthopedic surgery.[125] This trial evaluated patients who had hip fracture surgery and compared warfarin to no prophylaxis. In patients who received warfarin versus no prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)].

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[44] In this trial, a venous foot pump was compared to no prophylaxis in patients who had total knee replacement surgery. The risk of pulmonary embolism could not be calculated because no events occurred in either group compared.

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

Fatal pulmonary embolism

Pharmacologic prophylaxis versus no prophylaxis. Five trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery with the trials by Fuji and Powers and colleagues each including

two separate comparisons.[35,37,42,46,125] Four trials were excluded from the analysis because no events occurred in the groups compared, leaving one comparison from the trial by Powers and colleagues.[125] In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].

When limiting the original analysis to trials comparing pharmacologic prophylaxis to truly no prophylaxis, two trials remained with the trial by Powers and colleagues including two separate comparisons.[42,125] One trial and one comparison from Powers and colleagues were excluded because no events occurred in the groups compared, leaving the comparison of aspirin versus no prophylaxis from Powers and colleagues. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)]. Only one trial was conducted from 2001-present, by Fuji and colleagues, and no events occurred in either comparison in this trial, therefore subgroup analysis was not possible.[46] Subgroup analyses based on total hip replacement surgery[35,37,42] and total knee replacement surgery[46] were not possible because the included trials had no events in either groups compared. When limiting the original analysis to hip fracture surgery one trial by Powers and colleagues remained, with two separate comparisons included.[125] However in the comparison of warfarin to no prophylaxis no events occurred, leaving the comparison of aspirin to no prophylaxis. In this comparison, in patients receiving pharmacologic prophylaxis versus no prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[136] This study was conducted in patients who had total hip or total knee replacement surgery and included two separate comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of fatal pulmonary embolism could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significantly different in the occurrence of fatal pulmonary embolism (0.07 percent versus 0 percent, p= 0.189).

Oral antiplatelet agents versus no prophylaxis. One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery. In this trial patients who had hip fracture surgery received either aspirin or no prophylaxis and the odds of fatal pulmonary embolism were not significantly different [OR 7.06 (0.14 to 356.21)].[125]

One controlled observational study by Cusick and colleagues compared oral antiplatelet prophylaxis versus no prophylaxis and the results were previously described above.[136]

Injectable low molecular weight heparins versus no prophylaxis. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[35,37,42] The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[46] This trial evaluated patients who had total knee replacement and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral vitamin K antagonists versus no prophylaxis. One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of vitamin K antagonists versus no prophylaxis in patient who had major orthopedic surgery.[125] This trial evaluated patients who had hip fracture surgery and received either warfarin or no prophylaxis. The risk of fatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

One controlled observational study by Cusick and colleagues compared oral vitamin K antagonists versus no prophylaxis and the results were previously described above.[136]

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[44] In this trial, a venous foot pump was compared to no prophylaxis in patients who had total knee replacement surgery. The risk of fatal pulmonary embolism could not be calculated because no events occurred in either group compared.

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

Nonfatal pulmonary embolism

Pharmacologic prophylaxis versus no prophylaxis. Five randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery with the trials by Fuji and Powers and colleagues each including two separate comparisons.[35,37,42,46,125] Two trials were excluded from the analysis because no events occurred in either of the groups compared.[37,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.21 (0.04 to 1.30)] (Appendix Figure 10). Statistical heterogeneity was not detected (I^2 = 0 percent) although publication bias was detected (Egger's p-value = 0.009).

When limiting the analysis to trials which compared pharmacologic prophylaxis to truly no prophylaxis, two trials remained, with the trial by Powers and colleagues including two separate

comparisons.[42,125] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 0.21 (0.03 to 1.29)] (Appendix Figure 11). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis of trials published from 2001-present was not possible because only one trial remained and no events occurred in either of the groups compared.[46] When limiting the original analysis to total hip replacement, three trials remained although the trial by Samama and colleagues was excluded because no events occurred.[35,37,42] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.53 (0.06 to 5.09)] (Appendix Figure 12). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis of trials evaluating total knee replacement was not possible because only one trial remained and no events occurred in either of the groups compared.[46] When limiting the original analysis to hip fracture surgery, one trial remained by Powers and colleagues which included two separate comparisons.[125] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 0.16 (0.02 to 1.53)] (Appendix Figure 13). Statistical heterogeneity could not be evaluated because of too few studies.

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[136] This study was conducted in patients who had total hip or total knee replacement surgery and included two separate comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of nonfatal pulmonary embolism could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significant difference in the occurrence of nonfatal pulmonary embolism (0.67 percent versus 0 percent, p= 0.683).

Oral antiplatelet agents versus no prophylaxis. One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery. In this trial patients who had hip fracture surgery received either aspirin or no prophylaxis and the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)].[125] One controlled observational study by Cusik and colleagues also evaluated the impact of oral antiplatelet prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery and the results are presented above.[136]

Injectable low molecular weight heparins versus no prophylaxis. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[35,37,42] One trial was excluded from the analysis because no events occurred in either group compared.[37] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.53 (0.06 to 5.09)] (Appendix Figure 12). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[46] This trial evaluated patients who had total knee replacement surgery and included two separate comparisons; dabigatran 150mg daily and dabigatran 220mg daily each versus placebo. The risk of nonfatal pulmonary embolism could not be calculated because no events occurred in the groups compared.

Oral vitamin K antagonists versus no prophylaxis. One comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral vitamin K antagonists versus no prophylaxis in patient who had major orthopedic surgery.[125] This trial evaluated patients who had hip fracture surgery and received either warfarin or no prophylaxis. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.09)]. One controlled observational study by Cusik and colleagues also evaluated the impact of oral vitamin K antagonist prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery and the results are presented above.[136]

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial evaluated the impact of mechanical prophylaxis versus no prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[44] In this trial, a venous foot pump was compared to no prophylaxis in patients who had total knee replacement. The risk of nonfatal pulmonary embolism could not be calculated because no events occurred in either group compared.

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

Postthrombotic syndrome

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

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

Mortality

Pharmacologic prophylaxis versus no prophylaxis. Nine randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on mortality in patients who had major orthopedic surgery,[33,35-38,40,42,46,125] of which the trials by Fuji and Powers and colleagues each included two separate comparisons. Three trials were excluded from the analysis because no events occurred in the groups compared.[36,37,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality were not significantly different [OR 1.23 (0.54 to 2.78)] (Appendix Figure 14). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.757).

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared to truly no prophylaxis, five trials remained, with the trial by Powers and colleagues including two separate comparisons.[33,36,40,42,125] The trial by McKenna and colleagues was excluded from the analysis because no events occurred in either of the groups compared. In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of mortality were not significantly different [OR 1.26 (0.52 to 3.11)] (Appendix Figure 15). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis of trials published from 2001-present was not possible because only one trial remained and no events occurred in the groups compared.[46] When limiting original pooled analysis to trials conducted in patients who had total hip replacement surgery, five trials remained.[35,37,38,40,42] The trial by Samama and colleagues was excluded from the analysis because no events occurred in either of the groups compared. In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality were not significantly different [OR 1.02 (0.21 to 5.10)] (Appendix Figure 16). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting original pooled analysis to trials conducted in patients who had total knee replacement surgery, two trials remained and the risk of mortality could not be calculated because no events occurred in the groups compared.[36,46] When limiting the original pooled analysis to hip fracture surgery, two trials remained with the trial by Powers and colleagues including two separate comparisons.[33,125] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of mortality was not significantly different [RR 1.27 (0.50 to 3.26)] (Appendix Figure 17). Statistical heterogeneity was not detected (I^2 = 0 percent).

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

Two controlled observational studies evaluated the impact of pharmacologic prophylaxis versus no prophylaxis in patients who had major orthopedic surgery.[136,138] The first study by Cusick and colleagues evaluated patients who had either total hip or total knee replacement surgery and included two comparisons; warfarin versus no prophylaxis and aspirin versus no prophylaxis. Since no events occurred in either the warfarin or control groups, the risk of mortality could not be calculated in this comparison. In patients who received aspirin prophylaxis versus control, there was no significant difference in the risk of mortality (0.32 percent versus 0 percent, p = 0.902). The second study by Sachs and colleagues evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis.[138] No statistically significant difference in mortality was observed in this study when comparing patients who received warfarin versus no prophylaxis (0.1 percent versus 0.3 percent, p = 0.863).

Oral antiplatelet agents versus no prophylaxis. Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on mortality in patients who had major orthopedic surgery.[36,125] The trial by McKenna and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving one comparison from the trial by Powers and colleagues. The comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of aspirin versus placebo on mortality in patients who had major orthopedic surgery. In this comparison, the odds of mortality were not significantly different in patients receiving oral antiplatelet agents versus no prophylaxis [OR 1.62 (0.39 to 6.72)].

One controlled observational study by Cusick and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis and the results have been previously described above.[136]

Injectable low molecular weight heparins versus no prophylaxis. Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on mortality in patients who had major orthopedic surgery.[29,33,35,37,39,40,42] Two trials were excluded from the pooled analysis because no events occurred in either group.[29,37] In patients who received injectable low molecular weight heparin versus no prophylaxis, the odds of mortality were not significantly different [OR 0.98 (0.32 to 3.01)] (Appendix Figure 18). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.962).

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on mortality in patients who had major orthopedic surgery.[46] In this trial, patients who had total knee replacement were randomized to either dabigatran 150mg daily, dabigatran 220mg daily or placebo. The risk of mortality could not be calculated because no events occurred in the groups compared.

Oral vitamin K antagonists versus no prophylaxis. One comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of warfarin versus no prophylaxis on mortality in patients who had major orthopedic surgery.[125] In this comparison, the odds of mortality in patients receiving warfarin compared to no prophylaxis were not significantly different [OR 1.64 (0.39 to 6.84)].

Two controlled observational studies evaluated the impact of oral vitamin K antagonists versus no prophylaxis and the results have been previously described above.[136,138]

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

Mortality due to bleeding

Pharmacologic prophylaxis versus no prophylaxis. Eight randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery with the trials by Fuji and Powers and colleagues each included two separate comparisons.[33,36-38,40,42,46,125] Seven trials were excluded from the analysis because no events occurred in the groups compared,[33,36-38,40,46,125] leaving the trial by Turpie and colleagues which compared enoxaparin with placebo.[42] In this trial, in patients who received enoxaparin versus placebo the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)].

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared to truly no prophylaxis, five trials remained, with the trial by Powers and colleagues including two separate comparisons.[33,36,40,42,125] Four trials were excluded from the analysis because no events occurred in the groups compared,[33,36,40,125] leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.[42] In this trial, in patients who received enoxaparin versus placebo, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. Subgroup analysis based on trials published from 2001-present was not possible because only one trial remained and no events occurred in the groups compared.[46] When limiting original pooled analysis to trials conducted in patients who had total hip replacement surgery, four trials remained.[37,38,40,42] Three trials were excluded because no events occurred in the groups compared,[37,38,40] leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.[42] In this trial, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. When limiting the original pooled analysis to trials conducted in patients who had total knee replacement surgery, two trials remained and the trial by Fuji and colleagues included two separate comparisons.[36,46] The risk of mortality due to bleeding could not be calculated because no event occurred in the groups compared. When limiting the original pooled analysis to trials conducted in patients who had hip fracture surgery, two trials remained with the trial by Powers and colleagues contributing two separate comparisons of aspirin to placebo and warfarin to placebo.[33,125] No events occurred in either trial group therefore the risk of mortality due to bleeding could not be calculated.

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

Oral antiplatelet agents versus no prophylaxis. One randomized controlled trial by McKenna and colleagues as well as one comparison from the randomized controlled trial by Powers and colleagues evaluated the impact of oral antiplatelet agents versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[36,125] No events occurred in either trial therefore the risk of mortality due to bleeding could not be calculated.

Injectable low molecular weight heparins versus no prophylaxis. Five randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on

mortality due to bleeding in patients who had major orthopedic surgery.[33,37,38,40,42] Four trials were excluded from the pooled analysis because no events occurred in either group,[33,37,38,40] leaving the trial by Turpie and colleagues which compared enoxaparin to placebo.[42] In this trial, the odds of mortality due to bleeding in patients receiving enoxaparin versus placebo were not significantly different [OR 0.14 (0.003 to 6.82)].

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[46] In this trial, patients who had total knee replacement were randomized to either dabigatran 150mg daily, dabigatran 220mg daily or placebo. The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

Oral vitamin K antagonists versus no prophylaxis. One comparison within the randomized controlled trial by Powers and colleagues evaluated the impact of warfarin versus placebo on mortality due to bleeding in patients who had major orthopedic surgery.[125] No events occurred in either arm therefore the risk of mortality due to bleeding could not be calculated.

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

Health related quality of life

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

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

Deep vein thrombosis

Pharmacologic prophylaxis versus no prophylaxis. Sixteen randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery, with the three trial by trials by Fuji and colleagues and the trial by Alfaro and colleagues each including two separate comparisons.[28,29,31,33-38,40,42,43,45,46,126] In patients who received pharmacologic prophylaxis versus

no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.55 (0.45 to 0.67), NNT 3 to 11] (Appendix Figure 19). A higher level of statistical heterogeneity was detected but publication bias was not detected (I^2 = 56.6 percent, Egger's p-value = 0.080).

When limiting the original pooled analysis to trials in which pharmacologic prophylaxis was compared to truly no prophylaxis, nine trials remained, with the trial by Alfaro and colleagues including two separate comparisons.[28,29,33,34,36,40,42,43,126] In patients who received pharmacologic prophylaxis versus truly no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.44 (0.27 to 0.72), NNT 2 to 9] (Appendix Figure 20). A higher level of statistical heterogeneity was detected (I^2 = 69 percent). When limiting the original pooled analysis to trials published from 2001-present, four trials remained, with the three trials by Fuji and colleagues each including two separate comparisons.[29,31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.52 (0.43 to 0.64), NNT 4 to 10] (Appendix Figure 21). A lower level of statistical heterogeneity was detected (I^2 = 22.8 percent). When limiting the original pooled analysis to total hip replacement surgery, eleven trials remained,[28,31,34,35,37,38,40,42,43,45,126] of which the trials by Fuji and Alfaro and colleagues each included two separate comparisons. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.57 (0.43 to 0.75), NNT 3 to 11] (Appendix Figure 22). A higher level of statistical heterogeneity was detected (I^2 = 58.8 percent). When limiting original pooled analysis to total knee replacement, four trials remained,[29,31,36,46] of which the two trials by Fuji and colleagues each included two separate comparisons. In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.54 (0.40 to 0.73), NNT 3 to 10] (Appendix Figure 23). A higher level of statistical heterogeneity was detected (I^2 = 61.4 percent). When limiting the original pooled analysis to hip fracture surgery, one trial remained.[33] In this trial, the risk of developing deep vein thrombosis in patients who received pharmacologic prophylaxis versus no prophylaxis was significantly decreased [RR 0.35 (0.15 to 0.78), NNT 4].

Two randomized controlled trial evaluated the impact of age on the incidence of deep vein thrombosis in patients who had major orthopedic surgery.[34,36] The first trial by Kim and colleagues randomized patients to aspirin or no prophylaxis and performed subgroup analysis on the incidence of deep vein thrombosis based on patients with an age below 60 years versus age above 60 years. The incidence of deep vein thrombosis was not significantly different in the patients who received aspirin versus no prophylaxis in the subgroup aged below 60 years (p=0.426) or in the subgroup aged above 60 years (p=0.232).[34] The second trial by McKenna and colleagues randomized patients to aspirin or no prophylaxis. When adjusting for age, the odds of deep vein thrombosis were not significantly different in patients who received aspirin versus no prophylaxis [AOR 1.30 (-2.16 to 4.76)].[36]

The trial by Kim and colleagues also evaluated the impact of gender on the incidence of deep vein thrombosis in patients who received aspirin versus no prophylaxis.[34] There were no significant differences in the incidence of deep vein thrombosis in male patients (p=0.322) or in female patients (p=0.117) who received aspirin prophylaxis versus no prophylaxis. A second trial by Alfaro and colleagues found a significantly lower incidence of deep vein thrombosis in male patients who received aspirin prophylaxis versus no prophylaxis (0 percent versus 26 percent, p<0.04).

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

Oral antiplatelet agents versus no prophylaxis. Three randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery,[28,34,36] of which the trial by Alfaro and colleagues included two separate comparisons; aspirin 250mg per day versus no prophylaxis and aspirin 1 gram per day versus no prophylaxis. In patients who received oral antiplatelet agents versus no prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.41 (0.12 to 1.32)] (Appendix Figure 24). A higher level of statistical heterogeneity was detected as was the presence of publication bias (I^2 = 76 percent, Egger's p-value = 0.002).

Injectable low molecular weight heparins versus no prophylaxis. Eleven randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[29,31,33,35,37,38,40,42,45,126] The two trials by Fuji and colleagues included 2 separate comparisons of pharmacologic prophylaxis versus no prophylaxis. In patients who received low molecular weight heparin versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.53 (0.43 to 0.66), NNT 3 to 10] (Appendix Figure 25). A higher level of statistical heterogeneity was detected as was publication bias was detected (I^2 = 53.3 percent, Egger's p-value = 0.023).

Injectable unfractionated heparins versus no prophylaxis. One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[43] In this trial, the risk of deep vein thrombosis in patients receiving injectable unfractionated heparin compared to no prophylaxis was not significantly different [RR 1.60 (0.66 to 4.05)].

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[46] In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.51 (0.37 to 0.69), NNT 4] (Appendix Figure 26). Statistical heterogeneity and publication bias could not be calculated because of too few studies. Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat.

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

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[30] In this trial,

patients who had total hip replacement received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also wore graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.26 (0.10 to 0.65), NNT 4].

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

Asymptomatic deep vein thrombosis

Pharmacologic prophylaxis versus no prophylaxis. Three randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery and the trial by Fuji and colleagues included two separate comparisons.[35,37,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.52 (0.40 to 0.69), NNT 4 to 6] (Appendix Figure 27). A lower level of statistical heterogeneity was detected although publication bias was not detected (I^2 = 32.7 percent, Egger's p-value = 0.168).

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible because all three trials allowed concurrent use of graduated compression stockings along with the intervention patients were randomized to.[35,37,46] When limiting the original analysis to trials published from 2001-present, one trial remained by Fuji and colleagues which included two separate comparisons; dabigatran 150mg daily or dabigatran 220mg daily versus no prophylaxis.[46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.37 to 0.67), NNT 4] (Appendix Figure 28). Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat. Statistical heterogeneity could not be calculated because there were too few studies. This is also the same result that is obtained when limiting the original analysis to total knee replacement surgery since the trial by Fuji and colleagues was the only trial which fit this subgroup.[46] When limiting the original analysis to total hip replacement, two trials remained.[35,37] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.52 (0.27 to 1.00)] (Appendix Figure 29). Statistical heterogeneity could not be calculated because there were too few studies. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

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

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

Injectable low molecular weight heparins versus no prophylaxis. Two trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on asymptomatic deep

vein thrombosis in patients who had major orthopedic surgery.[35,37] Both of these trials were conducted in patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparins versus no prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.52 (0.27 to 1.00)] (Appendix Figure 29). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[46] In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.37 to 0.67), NNT 4] (Appendix Figure 28). Statistical heterogeneity and publication bias could not be calculated because of too few studies. Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat.

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

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

Symptomatic deep vein thrombosis

Pharmacologic prophylaxis versus no prophylaxis. Three randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery and the trial by Fuji and colleagues included two separate comparisons.[35,37,46] One trial was excluded from the analysis because no events occurred in either of the groups compared.[35] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.79 (0.17 to 3.73)] (Appendix Figure 30). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias could not be evaluated because of too few studies.

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible because all three trials allowed concurrent use of graduated

compression stockings along with the intervention patients were randomized to.[35,37,46] When limiting the original analysis to trials published from 2001- present, one trial remained by Fuji and colleagues which included two separate comparisons; dabigatran 150mg daily or dabigatran 220mg daily versus no prophylaxis.[46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.72 (0.12 to 4.39)] (Appendix Figure 31). Statistical heterogeneity could not be calculated because there were too few studies. This is also the same result that is obtained when limiting the original analysis to trials in total knee replacement surgery since the trial by Fuji and colleagues was the only trial which fit this subgroup.[46] When limiting the original analysis to total hip replacement, two trials remained.[35,37] The trial by Lassen and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving the trial by Samama and colleagues.[35,37] In this trial, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.96 (0.06 to 15.52)]. Statistical heterogeneity could not be calculated because there were too few studies. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[138] This trial evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. No statistically significant difference in symptomatic deep vein thrombosis was observed in this study when comparing patients who received warfarin versus no prophylaxis (0.2 percent versus 0 percent, p = 0.568).

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

Injectable low molecular weight heparins versus no prophylaxis. Two trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[35,37] Both of these trials were conducted in patients who had total hip replacement surgery. The trial by Lassen and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving the trial by Samama and colleagues. In this trial, in patients who received injectable low molecular weight heparins versus no prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.96 (0.06 to 15.52)]. Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[46] In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.72 (0.12 to 4.39)] (Appendix Figure 31). Statistical heterogeneity and publication bias could not be calculated because of too few studies.

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

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

Proximal deep vein thrombosis

Pharmacologic prophylaxis versus no prophylaxis. Eleven randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery and the three trials by Fuji and colleagues each included two separate comparisons.[29,31,35-37,40,42,45,46,126] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.53 (0.39 to 0.73), NNT 6 to 79] (Appendix Figure 32). A lower level of statistical heterogeneity was detected as was the presence of publication bias (I^2 = 10.7 percent, Egger's p-value 0.001).

When limiting the original analysis to trials which compared pharmacologic prophylaxis to truly no prophylaxis, five trials remained.[29,36,40,42,126] In patients who received pharmacologic prophylaxis versus truly no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.46 (0.27 to 0.79), NNT 4 to 68] (Appendix Figure 33). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to trials published from 2001-present, four trials remained; the three trials by Fuji and colleagues each included two separate comparisons.[29,31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.39 (0.20 to 0.74), NNT 16 to 62] (Appendix Figure 34). Statistical heterogeneity was not detected (I^2 = 0 percent).

When limiting the original analysis to total hip replacement surgery, seven trials remained and the trial by Fuji and colleagues included two separate comparisons.[31,35,37,40,42,45,126] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.54 (0.37 to 0.79), NNT 4 to 27] (Appendix Figure 35). A lower level of statistical heterogeneity was detected (I^2 = 23.9 percent). When limiting the original analysis to total knee replacement surgery four trials remained and the two trials by Fuji and colleagues each included two separate comparisons.[29,31,36,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of proximal deep vein

thrombosis was significantly decreased [RR 0.43 (0.21 to 0.88), NNT 5 to 65] (Appendix Figure 36). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

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

Oral antiplatelet agents versus no prophylaxis. One randomized controlled trial evaluated the impact of oral antiplatelet agents versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.[36] In this trial, patients who had total knee replacement were randomized to either aspirin or no prophylaxis. In patients who received oral antiplatelet agents versus no prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.80 (0.25 to 2.31)].

Injectable low molecular weight heparins versus no prophylaxis. Nine trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.[29,31,35,37,40,42,45,126] The two trials by Fuji and colleagues each included two separate comparisons. In patients who received injectable low molecular weight heparins versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.53 (0.38 to 0.75), NNT 4 to 79] (Appendix Figure 37). A lower level of statistical heterogeneity was detected as was the presence of publication bias (I^2 = 14.3 percent, Egger's p-value = 0.003).

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.[46] In this trial patients who had total knee replacement were randomized to dabigatran 150mg daily, dabigatran 220mg daily or placebo. All patients were allowed to also receive elastic compression stockings. In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.21 (0.05 to 0.95), NNT 21] (Appendix Figure 38). Because both experimental arms of the trial shared one control group, a range could not be calculated for the number needed to treat. Statistical heterogeneity could not be evaluated because of too few studies.

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

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[30] In this trial, patients who had total hip replacement surgery received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also received graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.41 (0.10 to 1.72)].

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

Distal deep vein thrombosis

Pharmacologic prophylaxis versus no prophylaxis. Six randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[29,35-37,40,45] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.56 (0.38 to 0.82), NNT 7 to 25] (Appendix Figure 39). A lower level of statistical heterogeneity was detected but publication bias was not detected (I^2 = 15.4 percent, Egger's p-value = 0.666).

When limiting the original analysis to trials in which pharmacologic prophylaxis was compared to truly no prophylaxis, three trials remained.[29,36,40] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.57 (0.22 to 1.46) (Appendix Figure 40). A higher level of statistical heterogeneity was detected (I^2 = 66.8 percent). When limiting the original analysis to trials published from 2001-present, only one trial remained.[29] In this trial, in patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.24 (0.10 to 0.58), NNT 7]. When limiting the original analysis to total hip replacement surgery, four trials remained.[35,37,40,45] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.57 (0.38 to 0.86), NNT 10 to 26] (Appendix Figure 41). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery, two trials remained.[29,36] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk if distal deep vein thrombosis was not significantly different [RR 0.55 (0.10 to 3.19)] (Appendix Figure 42). Statistical heterogeneity could not be calculated because of too few strata. Subgroup analysis limited to hip fracture surgery was not possible because none of the trials were conducted in this surgical population.

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

Oral antiplatelet agents versus no prophylaxis. One randomized controlled trial evaluated the impact of oral antiplatelet agents versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[36] In this trial, patients who had total knee replacement were randomized to either aspirin or no prophylaxis. In patients who received oral antiplatelet agents

versus no prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 1.33 (0.45 to 3.84)].

Injectable low molecular weight heparins versus no prophylaxis. Five trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[29,35,37,40,45] In patients who received injectable low molecular weight heparins versus no prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.50 (0.34 to 0.73), NNT 9 to 22] (Appendix Figure 43). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.615).

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

Injectable or oral factor Xa antagonists versus no prophylaxis. No randomized controlled trials evaluated the impact of injectable or oral factor Xa antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

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

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

Mechanical prophylaxis versus no prophylaxis. One randomized controlled trial by Fordyce and colleagues in 1992 evaluated the impact of mechanical prophylaxis versus no prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[30] In this trial, patients who had total hip replacement surgery received either prophylaxis with a venous foot pump or no prophylaxis, although patients in both groups also received graduated compression stockings. In patients who received mechanical prophylaxis versus no prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.68 (0.14 to 3.26)].

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

Major bleeding

Pharmacologic prophylaxis versus no prophylaxis. Seven randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding in patients who had major orthopedic surgery.[31,34,37,42,46,125] The three trials by Fuji and colleagues in 2010 and 2008 and the trial by Powers and colleagues each included two separate comparisons.[31,46,125] The trial by Kim and colleagues was excluded from the analysis because no

events occurred in either group.[34] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.74 (0.36 to 1.51)] (Appendix Figure 44). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.707).

When limiting to trials that compared pharmacologic prophylaxis to truly no prophylaxis, four trials remained.[34,42,125] The trial by Powers and colleagues included two separate comparisons.[125] The trial by Kim and colleagues was excluded from the analysis because no events occurred in either group.[34] In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of major bleeding were not significantly different [OR 0.53 (0.17 to 1.64)] (Appendix Figure 45). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to trials published from 2001 to the present; three trials remained by Fuji and colleagues and all three trials included two separate comparisons.[31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR 0.87 (0.31 to 2.45)] (Appendix Figure 46). Statistical heterogeneity was not detected (I^2 = 0 percent).

When limiting the original analysis to total hip replacement surgery, four trials remained, with the trial by Fuji and colleagues providing two separate comparisons.[31,34,37,42] The trial by Kim and colleagues was excluded from the analysis because no events occurred in either group. In patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of major bleeding were not significantly different [OR 1.61 (0.44 to 5.83)] (Appendix Figure 47). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery, two trials remained by Fuji and colleagues and both trials provided two separate comparisons.[31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR 0.59 (0.18 to 1.95)] (Appendix Figure 48). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to hip fracture surgery, one trial by Powers and colleagues remained and provided two separate comparisons.[125] In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding were not significantly different [RR 0.55 (0.12 to 2.51)] (Appendix Figure 49). Statistical heterogeneity was not detected (I^2 = 0 percent).

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

Oral antiplatelet agents versus no prophylaxis. Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus no prophylaxis on major bleeding in patients undergoing major orthopedic surgery.[34,125] The trial by Kim and colleagues was excluded from the analysis because no events occurred in either group, leaving the trial by Powers and colleagues. In this trial, in patients who received pharmacologic prophylaxis versus no prophylaxis, the odds of major bleeding were not significantly different [OR 0.24 (0.05 to 1.22)].

Injectable low molecular weight heparins versus no prophylaxis. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on major bleeding in patients who had major orthopedic surgery with the trials by Fuji and colleagues including two separate comparisons.[31,37,42,46] In patients who received pharmacologic prophylaxis versus no prophylaxis, the risk of major bleeding was not significantly different [RR

0.78 (0.29 to 2.08)] (Appendix Figure 50). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.275).

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

Injectable or oral factor Xa antagonists versus no prophylaxis. No randomized controlled trials evaluated the impact of injectable or oral factor Xa antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on major bleeding in patients who had major orthopedic surgery and included two separate comparisons.[46] In patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.96 (0.09 to 10.73)] (Appendix Figure 51). Statistical heterogeneity and publication bias could not be calculated because of too few strata.

Oral vitamin K antagonists versus no prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonists versus no prophylaxis on major bleeding in patients undergoing major orthopedic surgery.[125] In patients who received oral vitamin K antagonist prophylaxis versus no prophylaxis the risk of major bleeding was not significantly different [RR 0.97 (0.29 to 3.19)].

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

Major bleeding leading to reoperation

Pharmacologic prophylaxis versus no prophylaxis. Two randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery on this outcome and the trial by Fuji and colleagues included two separate comparisons.[37,46] The trial by Samama and colleagues and the comparison of dabigatran 150mg versus placebo from the trial by Fuji and colleagues were excluded from the analysis because no events occurred in the groups compared. The comparison of dabigatran 220mg versus placebo from the trial by Fuji and colleagues which evaluated patients who had total knee replacement surgery remained. In this trial, patients were also allowed to receive elastic compression stockings. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.11 (0.14 to 358.50)].

Subgroup analysis limited to trials which compared pharmacologic prophylaxis to truly no prophylaxis was not possible since both trials allowed the use of elastic stockings.[37,46] When limiting the original analysis to trials published from 2001- present one trial remained and included two separate comparisons.[46] One comparison was excluded from the analysis because

no events occurred leaving the second comparison of dabigatran 220mg versus no prophylaxis. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.11 (0.14 to 358.50)]. This is also the same result that is obtained when limiting the original analysis to total knee replacement surgery. Subgroup analysis based on total hip replacement was not possible because one trial remained and no events occurred in the groups compared.[37] Subgroup analysis limited to hip fracture surgery was not possible because none of the studies were conducted in this surgical population.

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

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

Injectable low molecular weight heparins versus no prophylaxis. One randomized controlled trial evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.[37] However the risk of major bleeding leading to reoperation could not be calculated because no events occurred in the groups compared.

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

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

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of injectable or oral direct thrombin inhibitors versus no prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery and included two separate comparisons.[46] One comparison was excluded from the analysis because no events occurred leaving the second comparison of dabigatran 220mg versus no prophylaxis. In this comparison, in patients who received oral direct thrombin inhibitors versus no prophylaxis the risk of major bleeding leading to reoperation was not significantly different [OR 7.11 (0.14 to 358.50)].

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

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

Minor bleeding

Pharmacologic prophylaxis versus no prophylaxis. Five randomized controlled trials evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery, with the three trials by Fuji and colleagues each contributing two separate comparisons.[31,37,42,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.61 (1.12 to 2.32), number needed to harm (NNH) 4 to 166] (Appendix Figure 52). Statistical heterogeneity was not detected, but publication was detected (I^2 = 0 percent, Egger's p-value = 0.030).

When limiting the original analysis to trials that compared pharmacologic prophylaxis to truly no prophylaxis, one trial remained.[42] In patients who received pharmacologic prophylaxis versus truly no prophylaxis the odds of minor bleeding were not significantly different [OR 7.39 (0.15 to 372.38)]. When limiting the original analysis to trials published from 2001 to the present; the three trials by Fuji and colleagues remained and all three trials provided two separate comparisons.[31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the odds of minor bleeding were significantly increased [OR 1.84 (1.06 to 3.22), NNH 27 to 62] (Appendix Figure 53). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to trials that compared pharmacologic prophylaxis to no prophylaxis in patients undergoing total hip replacement surgery, three trials remained, with the trial by Fuji and colleagues providing two separate comparisons.[31,37,42] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.56 (1.02 to 2.39), NNH 7 to 181] (Appendix Figure 54). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to trials that compared pharmacologic prophylaxis to no prophylaxis in patients undergoing total knee replacement surgery, two trials remained, with both the trials by Fuji and colleagues providing two separate comparisons.[31,46] In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was not significantly different [RR 1.77 (0.89 to 3.49)] (Appendix Figure 55). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

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

Injectable low molecular weight heparins versus no prophylaxis. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery.[31,37,42] The two trials by Fuji and colleagues provided two separate comparisons. In patients who received pharmacologic prophylaxis versus no prophylaxis the risk of minor bleeding was significantly increased [RR 1.60 (1.07 to 2.37)] (Appendix Figure 56). Statistical heterogeneity was not detected, but publication bias was detected (I^2 = 0 percent, Egger's p-value = 0.051).

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

Injectable or oral factor Xa antagonists versus no prophylaxis. No randomized controlled trials evaluated the impact of injectable or oral factor Xa antagonists versus no prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable or oral direct thrombin inhibitors versus no prophylaxis. One randomized controlled trial evaluated the impact of oral direct thrombin inhibitors versus no prophylaxis on minor bleeding in patients who had major orthopedic surgery and included two separate comparisons.[46] In patients who received oral direct thrombin inhibitors versus no prophylaxis the odds of minor bleeding were not significantly different [OR 1.67 (0.73 to 3.84)] (Appendix Figure 57). Statistical heterogeneity and publication bias could not be calculated because of too few strata.

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

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

Surgical site bleeding

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

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

Bleeding leading to infection

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

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

Bleeding leading to transfusion

Pharmacologic prophylaxis versus no prophylaxis. One randomized controlled trial evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery and included two comparisons.[46] This trial evaluated patients who had total knee replacement and randomized patients to one of three groups; dabigatran 150mg daily, dabigatran 220mg daily or placebo. Patients were also allowed to receive elastic compression stockings. The comparison of dabigatran 150mg versus no prophylaxis was excluded from the analysis because no events occurred in the groups compared, leaving the dabigatran 220mg versus no prophylaxis comparison. In this comparison, in patients who received pharmacologic prophylaxis versus no prophylaxis the odds of bleeding leading to transfusion were not significantly different [OR 7.11 (0.14 to 358.50)]. Statistical heterogeneity and publication bias could not be calculated because of too few strata.

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.[138] This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. In patients who received warfarin versus no prophylaxis the risk of bleeding leading to transfusion was not significantly different (0.1 percent versus 0 percent, p = 0.921).

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

Heparin induced thrombocytopenia

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

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

Discomfort

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

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

Readmission

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on readmission in patients who had major orthopedic surgery.[138] This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. No statistically significant difference in readmission rate was observed when comparing patients who received warfarin to those who received control (1.8 percent versus 0.9 percent, $p = 0.171$).

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

Reoperation

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

One controlled observational study evaluated the impact of pharmacologic prophylaxis versus no prophylaxis on reoperation in patients who had major orthopedic surgery.[138] This study evaluated patients who had total knee replacement surgery and compared warfarin versus no prophylaxis. Patients who received warfarin prophylaxis had a significantly higher rate of reoperation compared to patients who received no prophylaxis (1.1 percent versus 0.3 percent, $p < 0.01$).

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

Table 10. Summary of results for key question 4*

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Symptomatic objectively confirmed VTE				
Pharmacologic versus no prophylaxis	0	---	---	---
Mechanical versus no prophylaxis	0	---	---	---
Major VTE				
Pharmacologic versus no prophylaxis	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)	NA
▪ 2001-present	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)	NA
▪ TKR	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR: 0.21 (0.05 to 0.95)	NA
Mechanical versus no prophylaxis	0	---	---	---
PE				
Pharmacologic versus no prophylaxis	11 RCTs	Yes	OR 0.38 (0.13 to 1.07)	0
▪ Comparing to truly no prophylaxis	5 RCTs	Yes	RR 0.30 (0.09 to 0.99)	0
▪ 2001-present	4 RCTs	Yes	OR 0.40 (0.04 to 3.68)	73.8
▪ THR	7 RCTs	Yes	OR 0.44 (0.12 to 1.66)	0
▪ TKR	3 RCTs	Yes	OR 0.31 (0.03 to 3.23)	0
▪ HFS	1 RCT (2 comp)	Yes	RR 0.30 (0.04 to 2.42)	NA
Oral antiplatelet agents versus no prophylaxis	2 RCTs	Yes	RR 0.35 (0.07 to 1.87)	0
Injectable low molecular weight heparin versus no prophylaxis	7 RCTs	Yes	OR 0.55 (0.16 to 1.94)	0
Injectable unfractionated heparin versus no prophylaxis	1 RCT	No	RR 0.33 (0.03 to 3.84)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	No events in groups compared	NA
Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
Mechanical versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Fatal PE				
Pharmacologic versus no prophylaxis	5 RCTs 1 OBS	No	Four trials had no events; the remaining trial showed OR 7.06 (0.14 to 356.21). The observational study was inconclusive.	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Comparing to truly no prophylaxis	2 RCTs	No	One trial and one comparison of one trial had no events; the remaining comparison showed OR 7.06 (0.14 to 356.21).	NA
▪ 2001-present	1 RCT 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
▪ THR	3 RCTs 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
▪ TKR	1 RCT 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
▪ HFS	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.06 (0.14 to 356.21).	NA
Oral antiplatelet agents versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	OR 7.06 (0.14 to 356.21). The observational study was inconclusive.	NA
Injectable low molecular weight heparin versus no prophylaxis	3 RCTs	No	No events in the groups compared	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	No events in the groups compared	NA
Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	No events in the groups compared. The observational study was inconclusive.	NA
Mechanical prophylaxis versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Nonfatal PE				
Pharmacologic versus no prophylaxis	5 RCTs	Yes	OR 0.21 (0.04 to 1.30)	0
▪ Comparing to truly no prophylaxis	2 RCTs	Yes	RR 0.21 (0.03 to 1.29)	0
▪ 2001-present	1 RCT	No	No events in the groups compared	NA
▪ THR	3 RCTs	Yes	OR 0.53 (0.06 to 5.09)	NA
▪ TKR	1 RCT	No	No events in the groups compared	NA
▪ HFS	1 RCT (2 comp)	Yes	RR 0.16 (0.02 to 1.53)	NA
Oral antiplatelet agents versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
Injectable low molecular weight heparin versus no prophylaxis	3 RCTs	Yes	OR 0.53 (0.06 to 5.09)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp)	No	OR 0.13 (0.01 to 2.09)	NA
Mechanical prophylaxis versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
PTS				
Pharmacologic versus no prophylaxis	0	---	---	---
Mechanical versus no prophylaxis	0	---	---	---
Mortality				
Pharmacologic versus no prophylaxis	9 RCTs 2 OBS	Yes (RCTs)	OR: 1.23 (0.54 to 2.78). Observational studies supported this finding.	0
▪ Comparing to truly no prophylaxis	5 RCTs	Yes	OR: 1.26 (0.52 to 3.11)	0
▪ 2001-present	1 RCT 2 OBS	No	No events in the groups compared. Observational studies showed no difference.	NA
▪ THR	5 RCTs 1 OBS	Yes	OR: 1.02 (0.21 to 5.10). Observational study was inconclusive.	0
▪ TKR	2 RCTs 2 OBS	No	No events in either arm. Observational studies showed no difference.	NA
▪ HFS	2 RCTs	Yes	RR: 1.27 (0.50 to 3.26)	0
Oral antiplatelet agents versus no prophylaxis	2 RCTs 1 OBS	No	One trial had no events; the remaining trial showed OR: 1.62 (0.39 to 6.72). The observational study was inconclusive.	0
Injectable low molecular weight heparin versus no prophylaxis	7 RCTs	Yes	OR: 0.98 (0.32 to 3.01)	0
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Oral vitamin K antagonists versus no prophylaxis	1 RCT (1 comp) 1 OBS	No	OR: 1.64 (0.39 to 6.84). The observational study showed no difference.	NA
Mechanical versus no prophylaxis	0	---	---	---
Mortality due to bleeding				
Pharmacologic versus no prophylaxis	8 RCTs	No	Seven trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
▪ Comparing to truly no prophylaxis	5 RCTs	No	Four trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
▪ 2001-present	1 RCT	No	No events in the groups compared	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ THR	4 RCTs	No	Three trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
▪ TKR	2 RCTs	No	No events in the groups compared	NA
▪ HFS	2 RCTs	No	No events in the groups compared	NA
Oral antiplatelet agents versus no prophylaxis	2 RCTs	No	No events in the groups compared	NA
Injectable low molecular weight heparin versus no prophylaxis	5 RCTs	No	Four trials had no events; the remaining trial showed OR 0.14 (0.003 to 6.82)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Oral vitamin K antagonists versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Mechanical prophylaxis versus no prophylaxis	0	--	--	--
HRQOL				
Pharmacologic versus no prophylaxis	0	---	---	---
Mechanical versus no prophylaxis	0	---	---	---
DVT				
Pharmacologic versus no prophylaxis	16 RCTs	Yes	RR: 0.55 (0.45 to 0.67)	56.6
▪ Comparing to truly no prophylaxis	9 RCTs	Yes	RR: 0.44 (0.27 to 0.72)	69
▪ 2001-present	4 RCTs	Yes	RR: 0.52 (0.43 to 0.64)	28.8
▪ THR	11 RCTs	Yes	RR: 0.57 (0.43 to 0.75)	58.8
▪ TKR	4 RCTs	Yes	RR: 0.54 (0.40 to 0.73)	61.4
▪ HFS	1 RCT	No	RR: 0.35 (0.15 to 0.78)	---
▪ Age	2 RCTs	No	Age did not impact the effect of pharmacologic versus no prophylaxis on the risk of deep vein thrombosis.	NA
▪ Gender	2 RCTs	No	1 RCT showed no impact of gender although the other RCT showed decreased risk of DVT in male patients when comparing pharmacologic versus no prophylaxis	NA
Oral antiplatelet agents versus no prophylaxis	3 RCTs	Yes	RR: 0.41 (0.12 to 1.32)	76
Injectable low molecular weight heparin versus no prophylaxis	11 RCTs	Yes	RR: 0.53 (0.43 to 0.66)	53.3
Injectable unfractionated heparin versus no prophylaxis	1 RCT	No	RR: 1.60 (0.66 to 4.05)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.51 (0.37 to 0.69)	NA
Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.26 (0.10 to 0.65)	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.26 (0.10 to 0.65)	NA
Asymptomatic DVT				
Pharmacologic versus no prophylaxis	3 RCTs	Yes	RR 0.52 (0.40 to 0.69)	32.7
▪ 2001-present	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)	NA
▪ THR	2 RCTs	Yes	RR 0.52 (0.27 to 1.00)	NA
▪ TKR	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)	NA
Injectable low molecular weight heparin versus no prophylaxis	2 RCTs	Yes	RR 0.52 (0.27 to 1.00)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.50 (0.37 to 0.67)	NA
Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Symptomatic DVT				
Pharmacologic versus no prophylaxis	3 RCTs	Yes	OR 0.79 (0.17 to 3.73)	0
▪ 2001-present	1 RCT (2 comp)	Yes	RR 0.72 (0.12 to 4.39)	NA
▪ THR	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.96 (0.06 to 15.52)	NA
▪ TKR	1 RCT (2 comp)	Yes	RR 0.72 (0.12 to 4.39)	NA
Injectable low molecular weight heparin versus no prophylaxis	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.96 (0.06 to 15.52)	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.72 (0.12 to 4.39)	NA
Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Proximal DVT				
Pharmacologic versus no prophylaxis	11 RCTs	Yes	RR 0.53 (0.39 to 0.73)	10.7
▪ Comparing to truly no prophylaxis	5 RCTs	Yes	RR 0.46 (0.27 to 0.79)	0
▪ 2001-present	4 RCTs	Yes	RR 0.39 (0.20 to 0.74)	0
▪ THR	7 RCTs	Yes	RR 0.54 (0.37 to 0.79)	23.9

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ TKR	4 RCTs	Yes	RR 0.43 (0.21 to 0.88)	0
Oral antiplatelet agents versus no prophylaxis	1 RCT	No	RR 0.80 (0.25 to 2.31)	NA
Injectable low molecular weight heparin versus no prophylaxis	9 RCTs	Yes	RR 0.53 (0.38 to 0.75)	14.3
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.21 (0.05 to 0.95)	NA
Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.41 (0.10 to 1.72)	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.41 (0.10 to 1.72)	NA
Distal DVT				
Pharmacologic versus no prophylaxis	6 RCTs	Yes	RR 0.56 (0.38 to 0.82)	15.4
▪ Comparing to truly no prophylaxis	3 RCTs	Yes	RR 0.57 (0.22 to 1.46)	66.8
▪ 2001-present	1 RCT	No	RR 0.24 (0.10 to 0.58)	NA
▪ THR	4 RCTs	Yes	RR 0.57 (0.38 to 0.86)	0
▪ TKR	2 RCTs	Yes	RR 0.55 (0.10 to 3.19)	NA
Oral antiplatelet agents versus no prophylaxis	1 RCT	No	RR 1.33 (0.45 to 3.84)	NA
Injectable low molecular weight heparin versus no prophylaxis	5 RCTs	Yes	RR 0.50 (0.34 to 0.73)	0
Mechanical prophylaxis versus no prophylaxis	1 RCT	No	RR 0.68 (0.14 to 3.26)	NA
Venous foot pumps versus no prophylaxis	1 RCT	No	RR 0.68 (0.14 to 3.26)	NA
Major bleeding				
Pharmacologic versus no prophylaxis	7 RCTs	Yes	RR 0.74 (0.36 to 1.51)	0
▪ Comparing to truly no prophylaxis	4 RCTs	Yes	OR 0.53 (0.17 to 1.64)	0
▪ 2001-present	3 RCTs	Yes	RR 0.87 (0.31 to 2.45)	0
▪ THR	4 RCTs	Yes	OR 1.61 (0.44 to 5.83)	0
▪ TKR	2 RCTs	Yes	RR 0.59 (0.18 to 1.95)	0
▪ HFS	1 RCT (2 comp)	Yes	OR 0.55 (0.12 to 2.51)	0
Oral antiplatelet agents versus no prophylaxis	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.24 (0.05 to 1.22)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Injectable low molecular weight heparin versus no prophylaxis	4 RCTs	Yes	RR 0.78 (0.29 to 2.08)	0
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	RR 0.96 (0.09 to 10.73)	NA
Oral vitamin K antagonists versus no prophylaxis	1 RCT	No	RR 0.97 (0.29 to 3.19)	NA
Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Major bleeding leading to reoperation				
Pharmacologic versus no prophylaxis	2 RCTs	No	One trial and one comparison of one trial had no events; the remaining comparison of the second trial showed OR 7.11 (0.14 to 358.50)	NA
▪ 2001-present	1 RCT (2 comp)	No	One comparison of the trial had no events; the remaining comparison showed OR 7.11 (0.14 to 358.50)	NA
▪ THR	1 RCT	No	No events in the groups compared	NA
▪ TKR	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50)	NA
Injectable low molecular weight heparin versus no prophylaxis	1 RCT	No	No events in the groups compared	NA
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	No	One arm of the trial had no events; the remaining arm showed OR 7.11 (0.14 to 358.50)	NA
Mechanical prophylaxis versus no prophylaxis	0	---	---	---
Minor bleeding				
Pharmacologic prophylaxis versus no prophylaxis	5 RCTs	Yes	RR 1.61 (1.12 to 2.32)	0
▪ Comparing to truly no prophylaxis	1 RCT	No	OR 7.39 (0.15 to 372.38)	NA
▪ 2001-present	3 RCTs	Yes	OR 1.84 (1.06 to 3.22)	0
▪ THR	3 RCTs	Yes	RR 1.56 (1.02 to 2.39)	0
▪ TKR	2 RCTs	Yes	RR 1.77 (0.89 to 3.49)	0
Injectable low molecular weight heparin versus no prophylaxis	4 RCTs	Yes	RR 1.60 (1.07 to 2.37)	0
Injectable or oral direct thrombin inhibitors versus no prophylaxis	1 RCT (2 comp)	Yes	OR 1.67 (0.73 to 3.84)	NA

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

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

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

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

Key Question 5

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

Key Points

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

    - In a controlled observational study, oral antiplatelet agents had significantly higher mortality versus oral vitamin K antagonists in total hip or total knee replacement surgeries in one study but another study limited to total knee replacement found no significant differences.
    - In a controlled observational study, injectable low molecular weight heparin agents had significantly higher mortality versus injectable or oral factor Xa inhibitors in total hip, knee replacement and hip fracture surgeries.
    - In a controlled observational study, the use of an injectable factor Xa inhibitor was associated with a lower mortality than injectable unfractionated heparin.
- In the base case analysis, oral antiplatelet agents had significantly more deep venous thrombosis events versus mechanical prophylaxis.
    - Oral antiplatelet agents had significantly more deep venous thrombosis events versus mechanical prophylaxis in total knee replacement surgery.
- In the base case analysis, injectable low molecular weight heparin agents had significantly fewer deep venous thrombosis events versus unfractionated heparin.
    - Injectable low molecular weight heparin agents had significantly fewer deep venous thrombosis events versus injectable unfractionated heparin in total hip and total knee replacement surgeries.
    - Injectable low molecular weight heparin agents had significantly more deep venous thrombosis events versus injectable unfractionated heparin in hip fracture surgery.
    - No differences in efficacy between injectable low molecular weight or injectable unfractionated heparin was seen based on age, gender, or African American race but enoxaparin 30mg, but not 40mg, was superior to unfractionated heparin in preventing deep venous thrombosis in Caucasians.
- In the base case analysis, injectable low molecular weight heparins had significantly more deep venous thrombosis events versus injectable or oral factor Xa inhibitors.
    - In studies conducted from 2001 to the present, the same results occurred.
    - Injectable low molecular weight heparins had significantly more deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total hip replacement, total knee replacement, and hip fracture surgeries.
- In the base case analysis, injectable low molecular weight heparin agents had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors.
- In the base case analysis, injectable low molecular weight heparins had significantly fewer deep venous thrombosis events versus oral vitamin K antagonists.
    - There were higher levels of statistical heterogeneity but the direction of effect was similar in all trials.
    - Injectable low molecular weight heparins had significantly fewer deep venous thrombosis events versus oral vitamin K antagonists in trials conducted from 2001 to the present, total hip replacement and total knee replacement surgeries.
- In the base case analysis, injectable unfractionated heparin had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors.
    - Injectable unfractionated heparin had significantly more deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total hip replacement.
- In the base case analysis, injectable unfractionated heparin had significantly more deep venous thrombosis events versus mechanical prophylaxis.

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

    - Injectable low molecular weight heparin agents had significantly more distal deep venous thrombosis events versus injectable or oral factor Xa inhibitors in total hip replacement, total knee replacement, and hip fracture surgeries.
- In the base case analysis, injectable low molecular weight heparins had significantly fewer distal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors.
    - The same result occurred when limiting to studies from 2001 to the present.
    - Injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total knee replacement.
- In the base case analysis, injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus oral vitamin K antagonists.
    - The same result occurred when limiting to studies from 2001 to the present.
    - Injectable low molecular weight heparin agents had significantly fewer distal deep venous thrombosis events versus oral vitamin K antagonists in total hip replacement and total knee replacement surgeries.
- In the base case analysis, injectable low molecular weight heparin agents had significantly less major bleeding than injectable unfractionated heparin.
    - Injectable low molecular weight heparin agents had significantly less major bleeding than injectable unfractionated heparin in total hip replacement surgery.
- In the base case analysis, injectable low molecular weight heparin agents had significantly less major bleeding than injectable or oral factor Xa inhibitors.
    - The results were the same when limited to trials from 2001 to the present.
    - Injectable low molecular weight heparin agents had significantly less major bleeding than injectable or oral factor Xa inhibitors in total hip replacement surgery and total knee replacement surgery.
        - The different direction of effect between the total hip and knee replacement surgery trials versus the hip fracture surgery trials likely explains the higher level of statistical heterogeneity in the base case analysis.
- In the base case analysis, injectable low molecular weight heparin agents had significantly more major bleeding than oral vitamin K antagonists.
    - Injectable low molecular weight heparin agents had significantly more major bleeding than oral vitamin K antagonists in total hip replacement surgery and total knee replacement surgery.
- In the only evaluation available (a controlled observational study), major bleeding events were significantly increased in the group receiving injectable unfractionated heparin versus injectable or oral factor Xa inhibitors.
- In the base case analysis, injectable low molecular weight heparin agents had significantly less minor bleeding than injectable or oral factor Xa inhibitors.
    - The results were the same when limited to trials from 2001 to the present.
        - Injectable low molecular weight heparin agents had significantly less minor bleeding than injectable or oral factor Xa inhibitors in hip fracture surgery.
- In the base case analysis, injectable low molecular weight heparin agents had significantly more minor bleeding than oral vitamin K antagonists.

- In the base case analysis, injectable low molecular weight heparin agents had significantly more surgical site bleeding than injectable or oral direct thrombin inhibitors.
    - The same results occurred when trials were limited to 2001 to the present.
    - Injectable low molecular weight heparin agents had significantly more surgical site bleeding than injectable or oral direct thrombin inhibitors in total knee replacement surgery.
- In the base case analysis, injectable low molecular weight heparin agents had significantly more surgical site bleeding than oral vitamin K antagonists.
    - Injectable low molecular weight heparin agents had significantly more surgical site bleeding than oral vitamin K antagonists in total hip replacement surgery.
    - When major surgical site bleeding was evaluated for separately, injectable low molecular weight heparin agents had significantly more major surgical site bleeding than oral vitamin K antagonists.
- In the base case analysis, injectable low molecular weight heparin agents had significantly less heparin induced thrombocytopenia than injectable unfractionated heparin.
    - Injectable low molecular weight heparin agents had significantly less heparin induced thrombocytopenia than injectable unfractionated heparin in total hip replacement surgery.
- In the base case analysis, injectable low molecular weight heparin agents had significantly less discomfort than mechanical prophylaxis.
    - Injectable low molecular weight heparin agents had significantly less discomfort than mechanical prophylaxis in total hip replacement surgery.

Detailed Analysis

Study design and characteristics. Forty-four randomized controlled trials (N=35897) and three controlled observational studies (N=144806) evaluated the comparative efficacy between classes of pharmacologic prophylaxis and mechanical methods of prophylaxis on final health, intermediate and adverse outcomes.[48-51,53-62,64,66-70,72-79,81-83,86-92,94,95,97-99,125] All forty-four randomized controlled trials were published as full text manuscripts. Two randomized controlled trials compared oral antiplatelet agents to oral vitamin K antagonists[81,125] and two trials compared oral antiplatelet agents to mechanical methods of prophylaxis.[72,75] Fourteen trials compared injectable low molecular weight heparins to injectable unfractionated heparin,[48,50,54-56,64,67,79,82,86,89,90,97,98] five trials compared injectable low molecular weight heparin to injectable or oral factor Xa inhibitors,[51,57,76,92,99] five trials compared injectable low molecular weight heparins to injectable or oral direct thrombin inhibitors,[58-60,66,87] seven trials compared injectable low molecular weight heparins to oral vitamin K antagonist[53,68,70,73,74,77,78] and three trials compared injectable low molecular weight heparin to mechanical prophylaxis .[91,94,95] Two trials compared injectable unfractionated heparin to injectable or oral direct thrombin inhibitors[61,62] and one trial compared injectable unfractionated heparin to mechanical prophylaxis.[88] Three trials compared oral vitamin K antagonists to mechanical prophylaxis.[49,69,83]

Twenty-five trials enrolled exclusively patients who had total hip replacement surgery (N=20006),[48-50,53,54,56,60-62,64,66,69,70,74,76,79,82,83,86,88-92,94] eleven trials enrolled patients who had total knee replacement surgery (N=8185),[51,55,59,67,68,72,77,78,87,94,99] four trials enrolled patients who had hip fracture surgery (N=2155).[57,75,98,125] and four trials enrolled patients who had either total hip replacement surgery or total knee replacement surgery (N=4043).[58,73,81,97] The earliest trial was published in 1987 while the most recent published in 2009.[50,83,87] The duration of followup

ranged from the postoperative period to 180 days. Seven randomized controlled trials reported outcomes of interest during the postdischarge period[54,62,67,73,87,90]. Seventeen trials received funding from industry,[49,53,54,57-60,66-68,76,78,82,87,90,92,99] six trials received funding from government and foundation,[64,69,73,79,81,94] one trial received funding from industry and government,[125] one trial received funding from academia and industry,[74] two trials received funding from industry, government and foundation[83,125] and in eighteen trials the funding source was not reported.[48,50,51,55,56,61,62,70,72,75,77,86,88,89,91,95,97,98]

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

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

Of the three observational studies, two studies compared oral antiplatelet agents to oral vitamin K antagonists[136,140] and one study reported comparison between injectable low molecular weight heparin, injectable unfractionated heparin and injectable or oral factor Xa inhibitors.[139] One study enrolled only patients who had total knee replacement surgery (N=93840)[140] and another evaluated two surgical procedures and reported the outcomes separately for each; total hip replacement (N=2203) and total knee replacement surgery (N=2050).[136] The third study enrolled patients who had total hip replacement, total knee replacement, or hip fracture surgery (N=144806).[139] The most recent study was published in 2010 while the earliest study was published in 2007. The duration of followup for the studies ranged from 30 to 90 days. One study was funded by government and foundation[140] while the other two did not disclose the funding source.[136,139]

The mean age of patients ranged from 66.4 to 71 years. Females represented between 63.0 to 65.17 percent of the enrolled populations. Other baseline characteristics were not reported. Two studies enrolled exclusively patients who had primary surgery.[136,140] One study reported the surgical approach and for those who had total hip replacement, the posterior approach was used while for those who had total knee replacement the medial parapatellar approach was used.[136] Median hospital length of stay was reported in one study as 3 days.[140] Other procedural characteristics were not reported in these three studies.

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

Table 11 and an overall summary of results presented in

Table 12.

One trial by Eriksson and colleagues in 2005 was a dose finding study that evaluated the impact of four dabigatran doses (50mg twice daily, 150mg twice daily, 300mg daily or 225mg twice daily) versus enoxaparin on various outcomes of interest in patients who had either total hip or total knee replacement surgery.[58] When pooling trials that evaluated dabigatran in this report, the doses that have been evaluated in phase 3 trials were analyzed since dabigatran did not yet have Federal Drug Administration approval for venous thromboembolism. In this dose finding study, none of the regimens were those studied in phase 3 trials, and given the paucity of data comparing dabigatran to injectable low molecular weight heparin agents, the outcomes evaluated in this trial were discussed qualitatively.

Symptomatic objectively confirmed venous thromboembolism

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.[90] In this trial by Senaran and colleagues in 2006, patients who had total hip replacement surgery were randomized to receive either enoxaparin or unfractionated heparin prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 0.13 (0.01 to 2.15)]. Subgroup analyses were not possible because only one trial was available.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic objectively confirmed venous thromboembolism during the postdischarge period in patients who had total hip replacement surgery.[90] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the odds of symptomatic objectively confirmed venous thromboembolism during the postdischarge period were not significantly different [OR 7.54 (0.47 to 122.28)].

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic

objectively confirmed venous thromboembolism were not significantly different [OR 0.71 (0.49 to 1.04)] (Appendix Figure 58). A lower level of statistical heterogeneity was detected and a trend towards publication bias was detected (I^2 = 48.6 percent, Egger's p-value = 0.061). This is the same result obtained when limiting the analysis to trials published from 2001-present since all four trials fit this criterion. When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients with total hip replacement surgery who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the odds of symptomatic objectively confirmed venous thromboembolism were significantly decreased [OR 0.54 (0.33 to 0.89), NNT 75 to 219] (Appendix Figure 59). Statistical heterogeneity could not be calculated because of too few strata. When limiting the original analysis to total knee replacement surgery one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 1.97 (0.71 to 5.45)]. When limiting the original analysis to hip fracture surgery one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 0.75 (0.37 to 1.55)].

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.[53,78] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism were not significantly different [OR 1.00 (0.69 to 1.46)] (Appendix Figure 60). Statistical heterogeneity and publication bias could not be evaluated because of too few strata.

Subgroup analysis based on trials published from 2001-present was not possible since both trials were published prior to 2001. When limiting the original analysis to total hip replacement surgery one trial remained.[53] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 0.97 (0.66 to 1.41)]. When limiting the original analysis to total knee replacement surgery one trial remained.[78] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism was not significantly different [OR 2.71 (0.38 to 19.35)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on symptomatic objectively confirmed venous thromboembolism during the postdischarge period in patients who had major orthopedic surgery.[73] This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of symptomatic objectively confirmed venous thromboembolism during the postdischarge period were not significantly different [OR 2.24 (0.65 to 7.79)] (Appendix Figure 61). Similar results were seen when evaluating total hip replacement surgery [OR 2.74 (0.68 to 11.01)] or total knee replacement surgery [OR 1.02 (0.06 to 16.38)] separately.

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

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

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

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

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

Major venous thromboembolism

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

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

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

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major venous thromboembolism in patients who had major orthopedic surgery.[59,60] Two trials by Eriksson and colleagues each provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.26 (0.98 to 1.62)] (Appendix Figure 62). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.326).

When limiting the original analysis to trials published from 2001-present, two trials remained each including two separate comparisons.[59,60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.08 (0.78 to 1.50)] (Appendix Figure 63). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total hip replacement surgery two trials remained with one including two separate comparisons.[60,62] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.28 (0.94 to 1.76)] (Appendix Figure 64). A lower level of statistical heterogeneity was detected (I^2 = 18.6 percent). When limiting the original analysis to total knee replacement surgery one trial which included two separate comparisons remained.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major venous thromboembolism was not significantly different [RR 1.11 (0.63 to 1.96)] (Appendix Figure 65). Statistical heterogeneity could not be evaluated because of too few strata. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

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

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

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

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

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

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

Pulmonary embolism

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[125] In this trial by Powers and colleagues in 1989, patients who had hip fracture surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 7.28 (0.14 to 366.83)]. Subgroup analyses were not possible since this was the only trial available.

Oral antiplatelet agents versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[75] In this trial by Kennedy and colleagues in 2000, patients who had hip fracture surgery were randomized to receive either aspirin or venous foot pump prophylaxis. In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis the odds of pulmonary embolism were not significantly different [OR 7.09 (0.14 to 357.70)]. Subgroup analyses were not possible since this was the only trial available.

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on pulmonary embolism in patients who had major orthopedic surgery and one trial included two separate comparisons.[48,50,54,55,64,67,79,89,90,98] Four trials were excluded from the analysis because no events occurred in the groups compared.[50,67,89,90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.48 (0.24 to 0.95), NNT 8] (Appendix Figure 66). A range could not be calculated for the NNT because the lowest control event rate was zero. A higher level of statistical heterogeneity was detected although publication bias was not detected (I^2 = 59.7 percent, Egger's p-value = 0.623).

When limiting the original analysis to trials published from 2001-present one trial remained although no events occurred therefore the risk of pulmonary embolism could not be calculated.[90] When limiting the original analysis to total hip replacement surgery seven trials remained with one trial including two separate comparisons.[48,50,54,64,79,89,90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.28 (0.13 to 0.62), NNT 8] (Appendix Figure 67). A range could not be calculated for the NNT because the lowest control event rate was zero. Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery two trials remained.[55,67] One trial was excluded because no events occurred.[67] In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.13)]. When limiting the original analysis to hip fracture surgery one trial remained.[98] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of pulmonary embolism were significantly increased [OR 7.95 (1.53 to 41.29)]. The NNT could not be calculated because the control event rate was zero. Statistical heterogeneity could not be evaluated because of too few strata.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery.[54] This trial included two comparisons; enoxaparin 30mg every 12 hours or enoxaparin 40mg daily versus unfractionated heparin. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of pulmonary embolism during the postdischarge period was not significantly different [RR 0.13 (0.01 to 1.17)] (Appendix Figure 68).

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[99] In this trial by Bauer and colleagues in 2001, patients who had total knee replacement surgery were randomized to receive enoxaparin or fondaparinux prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of

pulmonary embolism were not significantly different [OR 3.34 (0.58 to 19.32)]. Subgroup analyses were not possible because this was the only trial available.

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[59,60 62] Two trials by Eriksson and colleagues each provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 1.18 (0.41 to 3.39)] (Appendix Figure 69). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.208).

When limiting the original analysis to trials published from 2001-present, two trials remained with each including two separate comparisons.[59,60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of pulmonary embolism was not significantly different [RR 1.25 (0.35 to 4.39)] (Appendix Figure 70). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total hip replacement surgery two trials remained with one including two separate comparisons.[60,62] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 1.03 (0.32 to 3.36)] (Appendix Figure 71). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery one trial which included two separate comparisons remained.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of pulmonary embolism was not significantly different [RR 2.00 (0.18 to 22.02)] (Appendix Figure 72). Statistical heterogeneity could not be evaluated because of too few strata. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on pulmonary embolism during the post discharge period in patients who had total hip replacement surgery.[66] In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of pulmonary embolism during the post discharge period were not significantly different [OR 3.89 (0.78 to 19.34)].

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Five randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[53,68,74,77,78] One trial included two separate comparisons although it was excluded from the analysis because no events occurred in the groups compared.[74] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.11 (0.57 to 2.19)] (Appendix Figure 73). A lower level of statistical heterogeneity was detected although the presence of publication bias was not detected (I^2 = 28.7 percent, Egger's p-value = 0.762).

When limiting the original analysis to trials published from 2001-present two trials remained.[68,77] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.96 (0.20 to 18.94)] (Appendix Figure 74). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total hip replacement surgery two trials remained with one trial including two separate comparisons, although this latter trial was excluded because no events occurred in the groups compared.[53,74] In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 1.23 (0.58 to 2.63)]. When limiting the original analysis to total knee replacement surgery three trials remained.[68,77,78] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.75 (0.17 to 3.31)] (Appendix Figure 75). A lower level of statistical heterogeneity was detected (I^2 = 48.2 percent). Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery.[73] This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of pulmonary embolism during the postdischarge period were not significantly different [OR 1.01 (0.06 to 16.14)] (Appendix Figure 76). Similar results were seen when evaluating total hip replacement surgery [OR 7.37 (0.15 to 371.45)] or total knee replacement surgery [OR 0.14 (0.003 to 6.97)] separately.

Injectable low molecular weight heparin agents versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery.[94] In this trial by Warwick and colleagues in 1998, patients who had total hip replacement surgery were randomized to receive enoxaparin or venous foot pump prophylaxis. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.72)]. Subgroup analyses were not possible because this was the only trial available.

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on pulmonary embolism in patients who had major orthopedic surgery.[61,62] In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of pulmonary embolism were not significantly different [OR 3.27 (0.56 to 18.98)] (Appendix Figure 77). Statistical heterogeneity and publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the analysis to total hip replacement surgery as both trials evaluated this surgical population. Subgroup analysis based on trials published from 2001-present was not possible as both trials were published prior to 2001. Subgroup analyses based on total knee

replacement or hip fracture surgery were not possible as no trials evaluated these surgical populations.

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

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on pulmonary embolism in patients who had major orthopedic surgery although no events occurred therefore the risk of pulmonary embolism could not be calculated.[83]

Fatal pulmonary embolism

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[125] This trial by Powers and colleagues in 1989 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.28 (0.14 to 366.83)]. Subgroup analyses were not possible as only one trial was available.

One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[136] This study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis. A significantly higher percent of patients who received aspirin prophylaxis had a fatal pulmonary embolism compared to those who received warfarin prophylaxis (0.07 percent versus 0 percent, $p<0.05$).

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[50,54,55,64,67,79,86,89,90,98] Nine trials were excluded from the analysis because no events occurred in the groups compared.[50,54,64,67,79,86,89,90,98] The remaining trial by Colwell and colleagues in 1995 evaluated

patients who had total knee replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.73)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.90 (0.38 to 2.13)] (Appendix Figure 78). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.744). This is the same result obtained when limiting the analysis to trials published from 2001 to the present.

When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.00 (0.14 to 7.10)] (Appendix Figure 79). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery, one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.00 (0.06 to 16.01)]. When limiting the original analysis to hip fracture surgery one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.87 (0.31 to 2.39)].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[59,60] The trials by Eriksson and colleagues in 2007 both provided two separate comparisons.[59,60] One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total hip replacement was excluded from the analysis because no events occurred in either group.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 1.43 (0.08 to 24.82) (Appendix Figure 80). A lower level of statistical heterogeneity was detected (I^2 = 31.7 percent), but publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained that provided two separate comparisons, one comparison was excluded from the analysis because no events occurred in either group.[60] In the remaining comparison, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin

inhibitor prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.91)]. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of fatal pulmonary embolism was not significantly different [RR 4.00 (0.36 to 44.03)] (Appendix Figure 81). Statistical heterogeneity could not be evaluated because of too few strata. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery.[66] In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of fatal pulmonary embolism during the postdischarge period were not significantly different [OR 0.14 (0.003 to 6.97)].

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[53,73,77,78] Three trials were excluded from the analysis because no events occurred in either group.[73,77,78] The remaining trial by Colwell and colleagues in 1994 evaluated patients who had total hip replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 7.29 (0.14 to 367.30)]. Subgroup analyses were not possible as only one trial with events was available.

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on fatal pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.[73]

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on fatal pulmonary embolism in patients who had major orthopedic surgery.[94,95] One trial was excluded from the analysis because no events occurred in either group compared.[94] The remaining trial by Warwick and colleagues in 2002 evaluated patients who had total knee replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.25)]. Subgroup analyses were not possible as only one trial with events was available.

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin prophylaxis versus oral direct thrombin inhibitor prophylaxis on fatal pulmonary embolism in

patients who had major orthopedic surgery although no events occurred in either trial so the risk of fatal pulmonary embolism could not be evaluated.[61 62]

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery although no events occurred in either group so the risk of fatal pulmonary embolism could not be evaluated.[83]

Nonfatal pulmonary embolism

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet agent prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery. However, no events occurred in either group and the risk of nonfatal pulmonary embolism could not be evaluated.[125]

One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[136] This study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis. There was no significant difference in the percent of patients who had a nonfatal pulmonary embolism comparing aspirin to warfarin prophylaxis (0.67 percent versus 0 percent, $p = 0.112$).

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Ten randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[50,54,55,64,67,79,86,89,90,98] Four trials were excluded from the analysis because no events occurred in the groups compared.[50,67,89,90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.50 (0.25 to 1.00)] (Appendix Figure 82). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 58.8 percent, Egger's p-value = 0.634).

When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared therefore the risk of nonfatal pulmonary embolism could not be evaluated.[90] When limiting the original analysis to total hip replacement surgery seven trials remained.[50,54,64,79,86,89,90] Three trials were excluded from the analysis because no events occurred in the groups compared.[50,89,90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.28 (0.13 to 0.62), NNT 6] (Appendix Figure 83). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery two trials remained.[55,67] One trial was excluded from the analysis because no events occurred in either group compared.[67] In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.73)]. When limiting the original analysis to hip fracture surgery one trial remained.[98] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of nonfatal pulmonary embolism were significantly increased [OR 7.95 (1.53 to 41.29)]. The number needed to harm could not be calculated because the control event rate was zero.

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

One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on nonfatal pulmonary embolism during the postdischarge period in patients who had total hip replacement surgery.[54] In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin 30mg every 12 hours, enoxaparin 40mg daily or unfractionated heparin prophylaxis. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of nonfatal pulmonary embolism during the postdischarge period was not significantly different [RR 0.13 (0.01 to 1.17)] (Appendix Figure 68).

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.68 (0.34 to 1.37)] (Appendix Figure 84). A lower level of statistical heterogeneity and the presence of publication bias were detected (I^2 = 49.5 percent, Egger's p-value = 0.040). This is the same result obtained when limiting the analysis to trials published from 2001 to the present.

When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.39 (0.16 to 0.95), NNT 166 to 833] (Appendix Figure 85). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery one trial remained.[99] In this trial, in patients

who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.95 (0.39 to 9.72)]. When limiting the original analysis to hip fracture surgery one trial remained.[57] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.32 (0.30 to 5.81)].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery, and both trials included two separate comparisons.[59,60] One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total knee replacement was excluded from the analysis because no events occurred in either group.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.92 (0.23 to 3.66)] (Appendix Figure 86). A higher level of statistical heterogeneity was detected (I^2 = 53.7 percent), but publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the analysis to trials published from 2001 to the present.

When limiting the original analysis to total hip replacement surgery one trial remained that included two separate comparisons.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of nonfatal pulmonary embolism was not significantly different [RR 1.61 (0.13 to 19.37)] (Appendix Figure 87).] Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained. [59] One arm of the trial by Eriksson and colleagues in 2007 comparing 220mg of dabigatran to injectable low molecular weight heparin in patients undergoing total knee replacement was excluded from the analysis because no events occurred in either group.[59] In the remaining comparison, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.93)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Three randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[73,77,78] The trial by Hull and colleagues in 1993 provided two separate comparisons, however the trial was excluded from the analysis because no events occurred in either comparison.[73] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary

embolism were not significantly different [OR 1.00 (0.20 to 4.95)] (Appendix Figure 88). Statistical heterogeneity and publication bias could not be evaluated because of too few strata.

When limiting the original analysis to trials published from 2001-present one trial remained.[77] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 7.46 (0.46 to 120.00)]. When limiting the original analysis to total hip replacement surgery one trial, contributing two separate comparisons remained, however no events occurred in any of the groups compared therefore the risk of nonfatal pulmonary embolism could not be calculated.[73] When limiting the original analysis to total knee replacement, two trials remained.[77,78] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 1.00 (0.20 to 4.95)] (Appendix Figure 89). Statistical heterogeneity and publication bias could not be evaluated because of too few strata. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis on nonfatal pulmonary embolism during the postdischarge period in patients who had major orthopedic surgery.[73] This trial evaluated patients who had total hip or total knee replacement surgery and reported results separately. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of nonfatal pulmonary embolism during the postdischarge period were not significantly different [OR 1.01 (0.06 to 16.14)] (Appendix Figure 90). Similar results were seen when evaluating total hip replacement surgery [OR 7.37 (0.15 to 371.45)] or total knee replacement surgery [OR 0.14 (0.003 to 6.97)] separately.

Injectable low molecular weight heparin agents versus mechanical prophylaxis. One randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[94] In this trial by Warwick and colleagues in 1998, patients who had total hip replacement surgery were evaluated. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.72)]. Subgroup analyses were not possible as only one trial was available.

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin prophylaxis versus oral direct thrombin inhibitor prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[61,62] In patients who received injectable unfractionated heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the odds of nonfatal pulmonary embolism were not significantly different [OR 3.27 (0.56 to 18.98)] (Appendix Figure 91). Statistical heterogeneity and publication bias could not be evaluated because of too few strata. This is the same result for trials limited to total hip replacement surgery. Subgroup analysis based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery was not possible because no trials fit these criteria.

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

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on nonfatal pulmonary embolism in patients who had major orthopedic surgery although no events occurred in either group so the risk of nonfatal pulmonary embolism could not be evaluated.[83]

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

Mortality

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on mortality in patients who had major orthopedic surgery.[125] In this trial by Powers and colleagues in 1989, patients who had hip fracture surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of mortality was not significantly different [RR 0.98 (0.32 to 3.05)]. Subgroup analyses were not possible as this was the only trial available.

Two controlled observational studies evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on mortality in patients who had major orthopedic surgery.[136,140] The first study evaluated patients who had total hip replacement or total knee replacement surgery and who received aspirin or warfarin prophylaxis.[136] A significantly higher percent of patients who received aspirin prophylaxis died compared to those who received warfarin prophylaxis (0.3 percent versus 0 percent, $p = 0.013$). The second study evaluated patients who had total knee replacement surgery and who received either aspirin or warfarin prophylaxis.[140] The odds of mortality for patients who received warfarin versus aspirin prophylaxis were not significantly different [AOR 0.54 (0.25 to 1.15)].

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Eight randomized controlled trials evaluated the impact of injectable low molecular weight heparins versus injectable unfractionated heparin on mortality in patients who had major orthopedic surgery with one trial by Colwell and colleagues including two separate comparisons.[50,54,64,79,86,89,90,98] Five trials were excluded from the analysis because no events occurred in the groups compared.[50,79,86,89,90] In patients who received injectable low molecular weight heparins versus injectable unfractionated heparin the odds of mortality were not significantly different [OR 0.39 (0.10 to 1.49)] (Appendix Figure 92). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.102).

When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared therefore risk of mortality could not be calculated.[90] When limiting the original analysis to total hip replacement surgery, seven trials remained, with the trial by Colwell and colleagues including two separate comparisons. Five trials were excluded from the analysis because no events occurred in the groups compared. In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the odds of mortality in the two remaining trials were not significantly different [OR 0.21 (0.03 to 1.59)] (Appendix Figure 93). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis based on total knee replacement was not possible because no trials evaluated this surgical population. When limiting the original analysis to hip fracture surgery, one trial remained.[98] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of mortality was not significantly different [RR 0.64 (0.13 to 3.06)].

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on mortality in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.08 (0.72 to 1.60)].(Appendix Figure 94) Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.952). This is the same result obtained when limiting the analysis to trials published from 2001-present since all four trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, two trials remained.[76,92] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 0.88 (0.32 to 2.42)] (Appendix Figure 95). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial remained.[99] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.49 (0.26 to 8.65)]. When limiting the original analysis to hip fracture surgery, one trial remained.[57] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of mortality were not significantly different [OR 1.10 (0.70 to 1.72)].

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

One controlled observational study evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery.[139] This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either an injectable low molecular weight heparin (enoxaparin or dalteparin) or fondaparinux. Mortality was significantly decreased in patients who received fondaparinux (0.6 percent) versus injectable low molecular weight heparin (1.1 percent) ($p < 0.001$).

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on mortality in patients who had major orthopedic surgery with one trial by Ginsberg and two trials by Eriksson and colleagues including two separate comparisons.[59,87] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.45 (0.15 to 1.36)] (Appendix Figure 96). Statistical heterogeneity was not detected but the presence of publication bias was detected ($I^2 = 0$ percent, Egger's p-value = 0.023).

When limiting the original analysis to trials published from 2001-present, three trials remained with all three trials including two separate comparisons.[59,60,87] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.54 (0.15 to 1.98)] (Appendix Figure 97). Statistical heterogeneity was not detected ($I^2 = 0$ percent). When limiting the original analysis to total hip replacement surgery, two trials remained with one trial by Eriksson and colleagues in 2007 including two separate comparisons.[60,66] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.27 (0.06 to 1.23)] (Appendix Figure 98). Statistical heterogeneity was not detected ($I^2 = 0$ percent). When limiting the original analysis to total knee replacement surgery, two trials remained with both trials including two separate comparisons.[59,87] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of mortality was not significantly different [RR 0.80 (0.16 to 4.17)] (Appendix Figure 99). Statistical heterogeneity was not detected ($I^2 = 0$ percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared to enoxaparin in patients who had total hip or total knee replacement surgery.[58] During the treatment period, no deaths occurred in any of the groups however during the post treatment period, one death occurred in each of the dabigatran 50mg twice daily and dabigatran 225mg twice daily groups.

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Six randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on mortality in patients who had major orthopedic

surgery with one trial by Hull and colleagues including two separate comparisons.[53,68,73,74,77,78] One trial was excluded from the analysis because no events occurred in the groups compared.[77] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.79 (0.42 to 1.50)] (Appendix Figure 100). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.188)

When limiting the original analysis to trials published from 2001-present, two trials remained.[68,77] One trial was excluded from the analysis because no events occurred in the groups compared[77] leaving one trial for the analysis. In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.37 (0.05 to 2.66)]. When limiting the original analysis to total hip replacement surgery, two trials remained with one trial by Hull and colleagues including two separate comparisons.[53,74] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of mortality was not significantly different [RR 0.81 (0.36 to 1.82)] (Appendix Figure 101). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery, three trials remained.[68,77,78] One trial was excluded from the analysis because no events occurred in the groups compared.[77] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of mortality were not significantly different [OR 0.52 (0.10 to 2.57)] (Appendix Figure 102). Statistical heterogeneity was not evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.[94,95] In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR 0.31 (0.05 to 1.81)] (Appendix Figure 103). Statistical heterogeneity and publication bias were not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[95] In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR 0.38 (0.05 to 2.73)]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.[94] In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the odds of mortality were not significantly different [OR 0.14 (0.003 to 7.01)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin

versus injectable or oral direct thrombin inhibitors on mortality in patients who had major orthopedic surgery.[61,62] In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of mortality were not significantly different [OR 7.13 (0.74 to 68.80)] (Appendix Figure 104). Statistical heterogeneity and publication bias were not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery and hip fracture surgery were not possible because no trials fit these criteria.

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

Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors. One controlled observational study evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality in patients who had major orthopedic surgery.[139]This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either fondaparinux or injectable unfractionated heparin. Mortality was significantly decreased in patients who received fondaparinux (0.6 percent) versus injectable unfractionated heparin (2.2 percent) ($p< 0.001$ for both comparisons).

Injectable unfractionated heparin versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.[88] In this trial by Santori and colleagues in 1994, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or venous foot pump prophylaxis. In patients who received injectable unfractionated heparin versus mechanical prophylaxis, the odds of mortality were not significantly different [OR 7.62 (0.15 to 384.19)]. Subgroup analyses were not possible as this was the only trial available.

Oral vitamin K antagonists versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on mortality in patients who had major orthopedic surgery.[49,69] One trial was excluded from the analysis because no events occurred in the groups compared,[49] leaving the trial by Francis and colleagues in 1992.[69] In this trial, patients who had total hip replacement surgery were randomized to receive either warfarin or intermittent pneumatic compression prophylaxis. In patients who received oral vitamin K antagonist prophylaxis versus mechanical prophylaxis, the odds of mortality were not significantly different [OR 0.95 (0.06 to 15.33)]. Subgroup analyses were not possible as this was the only trial available.

Mortality due to bleeding

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery, however no events occurred and therefore the risk of mortality due to bleeding could not be calculated.[125]

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[50,64,79,86,89,90,98] Six trials were excluded from the pooled analysis because no events occurred in the groups compared.[50,64,79,86,89,90] The remaining trial by Monreal and colleagues in 1989 evaluated patients who had hip fracture surgery.[98] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.13 (0.003 to 6.52)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[57,76,92,99] Three trials were excluded from the pooled analysis because no events occurred in the groups compared.[76,92,99] The remaining trial by Eriksson and colleagues in 2001 evaluated patients who had hip fracture surgery.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 7.29 (0.14 to 367.58)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[59,60,87] Each trial included two separate comparisons, although two trials were excluded from the analysis because no events occurred in the groups compared.[59,87] The remaining trial by Eriksson and colleagues in 2007 evaluated patients who had total hip replacement surgery and included two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of mortality due to bleeding was not significantly different [RR 0.67 (0.07 to 6.40)] (Appendix Figure 105). Statistical heterogeneity and publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the original analysis to trials published from 2001-present as well as limiting the original analysis to total hip replacement surgery (Appendix Figure 106). No events occurred in the two trials evaluating patients who had total knee replacement surgery,[59,87] and no trials evaluated patients who had hip fracture surgery.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin

prophylaxis versus oral vitamin K antagonist prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[68,73,74,78] One trial included patients who had hip replacement or knee replacement surgery and presented outcomes separately for each surgery while another trial included two comparisons. However, both of these trials, along with a third, were excluded from the analysis because no events occurred in the groups compared.[73,74,78] The remaining trial by Fitzgerald and colleagues in 2001 evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 6.94)] in this trial. Subgroup analyses were not possible because only one trial with events was available.

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery.[94,95] One trial was excluded from the analysis because no events occurred in the groups compared, leaving one trial by Warwick and colleagues in 1998 that evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis, the odds of mortality due to bleeding were not significantly different [OR 0.14 (0.003 to 7.01)]. Subgroup analyses were not possible because only one trial with events was available.

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on mortality due to bleeding in patients who had major orthopedic surgery.[61,62] The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

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

Injectable unfractionated heparin versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of injectable unfractionated heparin prophylaxis versus mechanical prophylaxis on mortality due to bleeding. Since no events occurred in the groups compared, the risk of mortality due to bleeding could not be calculated.[88]

Oral vitamin K antagonists versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on mortality due to bleeding in patients who had major orthopedic surgery.[49,69] The risk of mortality due to bleeding could not be calculated because no events occurred in the groups compared.

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

Deep vein thrombosis

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on deep vein thrombosis in patients who had major orthopedic surgery.[81] In this trial by Lotke and colleagues in 1996, patients who had total hip replacement or total knee replacement surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.06 (0.87 to 1.30)]. Subgroup analyses were not possible as this was the only trial available. This trial also evaluated the impact of gender on the development of deep vein thrombosis in patients treated with aspirin or warfarin prophylaxis and reported no significant differences between males and females.

Oral antiplatelet agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery with one trial by Hass and colleagues including two surgical populations; unilateral or bilateral total knee replacement.[72,75] In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 1.63 (1.11 to 2.39), NNH 4 to 27] (Appendix Figure 107). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias could not be evaluated because of too few studies.

Subgroup analyses based on trials published from 2001-present or total hip replacement surgery were not possible because no trials fit either of these criteria. When limiting the original analysis to total knee replacement surgery, one trial by Haas and colleagues which reported unilateral and bilateral total knee replacement surgery separately remained.[72] In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 1.63 (1.08 to 2.44), NNH 4 to 8] (Appendix Figure 108). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.[75] In patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.68 (0.55 to 5.19)].

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Fourteen randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on deep vein thrombosis in patients who had major orthopedic surgery with three trials including two separate comparisons.[48,50,54-56,64,67,79,82,86,89,90,97,98] The trial by Rader and colleagues was excluded from the pooled analysis because all patients received heparin prophylaxis pre- and postoperatively prior to being randomized to receive enoxaparin or unfractionated heparin.[97] When pooling the remaining thirteen trials, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.80 (0.65 to 0.99), NNT 12 to 100] (Appendix Figure 109). A lower level of statistical heterogeneity was detected although publication bias was not detected (I^2 = 34.3 percent, Egger's p-value = 0.808).

The trial by Rader and colleagues in 1998 that was excluded from the pooled analysis was evaluated separately.[97] This trial evaluated patients who had total hip or total knee replacement surgery and reported outcomes separately. In patients who received injectable low molecular weight prophylaxis versus injectable unfractionated heparin prophylaxis the risk of deep vein thrombosis was not significantly different [RR 3.37 (0.70 to 16.17)] (Appendix Figure 110). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Results were similar when evaluating the two surgical populations separately; total hip replacement [RR 1.60 (0.21 to 12.06)] and total knee replacement [RR 6.00 (0.99 to 37.43)].

When limiting the original pooled analysis of 13 trials to trials published from 2001-present, 1 trial remained.[90] In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of deep vein thrombosis were not significantly different [OR 0.13 (0.01 to 2.15)]. When limiting the original analysis to total hip replacement surgery, 10 trials remained, with 3 of the trials including two separate comparisons.[48,50,54,56,64,79,82,86,89,90] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.75 (0.58 to 0.97), NNT 12 to 100] (Appendix Figure 111). A lower level of statistical heterogeneity was detected (I^2 = 26.4 percent). When limiting the original analysis to total knee replacement surgery, two trials remained.[55,67] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of deep vein thrombosis was significantly decreased [RR 0.75 (0.58 to 0.96), NNT 12 to 16] (Appendix Figure 112). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.[98] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of deep vein thrombosis was significantly increased [RR 2.19 (1.01 to 4.98), NNH 5].

One trial that compared low molecular weight heparin to unfractionated heparin evaluated the impact of age, gender, and ethnicity on antithrombotic effect deep vein thrombosis.[54] No significant difference in the risk of deep vein thrombosis were found in patients who received low molecular weight heparin versus unfractionated heparin when evaluating those with an age less than 65 years, greater than 65 years, female gender, male gender, or black race. In patients of white race and randomized to enoxaparin 30mg twice daily versus unfractionated heparin, the risk of deep vein thrombosis was significant decreased (5 percent vs. 14 percent, p=0.03) although this effect was not seen when comparing enoxaparin 40mg daily to unfractionated heparin. Although the race categories of “Oriental/Asian” and “other” were also evaluated, risk could not be calculated because no events occurred in the groups compared. A second trial evaluated the impact of gender on the effect of prophylaxis in patients who received low molecular weight heparin versus unfractionated heparin and concluded that gender did not significantly impact the antithrombotic effect of the prophylactic regimens when evaluating deep vein thrombosis (40 percent females vs. 30 percent males, p=0.30).[64]

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on deep vein thrombosis in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors, the risk of deep vein thrombosis was significantly increased [RR 2.06 (1.66 to 2.55), NNH 8 to 24] (Appendix

Figure 113). A lower level of statistical heterogeneity was detected although publication bias was not detected (I^2 = 35.5 percent, Egger's p-value = 0.473). This is the same result obtained when limiting the analysis to trials published from 2001-present since all four trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, two trials remained.[76,92] In patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the odds of deep vein thrombosis were significantly increased [OR 1.87 (1.43 to 2.44), NNH 21 to 31] (Appendix Figure 114). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of deep vein thrombosis was significantly increased [RR 2.18 (1.59 to 3.01), NNH 8]. When limiting the original analysis to hip fracture surgery, one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the risk of deep vein thrombosis was significantly increased [RR 2.39 (1.75 to 3.28), NNH 9].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitors on deep vein thrombosis in patients who had major orthopedic surgery.[66] In this trial by Eriksson and colleagues in 1997, patients who had total hip replacement surgery were randomized to receive enoxaparin or desirudin prophylaxis. In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 1.39 (1.15 to 1.68), NNH 15]. Subgroup analyses were not possible as this was the only trial available.

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on deep vein thrombosis in patients who had major orthopedic surgery with one trial including two separate comparisons and another trial reporting two surgical populations separately.[68,70,73,74,78] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.66 (0.55 to 0.79), NNT 6 to 13] (Appendix Figure 115). A higher level of statistical heterogeneity and the presence of publication bias was detected (I^2 = 60.9 percent, Egger's p-value = 0.033). However, the direction of effect was similar in all trials and 4 of 5 trials and 1 of 2 arms in another trial found significant superiority of injectable low molecular heparins versus oral vitamin K antagonists individually. So heterogeneity is due to differences in the magnitude of benefit.

When limiting the original analysis to trials published from 2001-present, one trial remained.[68] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.57 (0.42 to 0.76), NNT 6]. When limiting the original analysis to total hip replacement surgery, three trials remained, with the one trial including two separate comparisons.[70,73,74] In patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.61 (0.44 to 0.84), NNT 10 to 12]

(Appendix Figure 116). A higher level of statistical heterogeneity was detected (I^2 = 67.6 percent). When limiting the original analysis to total knee replacement surgery, three trials remained.[68,73,78] In patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of deep vein thrombosis was significantly decreased [RR 0.71 (0.57 to 0.87), NNT 7 to 11] (Appendix Figure 117). A higher level of statistical heterogeneity was detected (I^2 = 57.2 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery. [91,94,95] In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.90 (0.71 to 1.14)] (Appendix Figure 118). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[95] In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.94 (0.72 to 1.21)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.[91,94] In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 0.75 (0.43 to 1.30)] (Appendix Figure 119). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin agents versus injectable or oral direct thrombin inhibitor prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[61,62] In patients who received injectable unfractionated heparin agents versus injectable or oral direct thrombin inhibitors, the risk of deep vein thrombosis was significantly increased [RR 2.31 (1.34 to 4.00) NNH 5 to 11] (Appendix Figure 120). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery were not possible because no trials fit these criteria.

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

Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors. No randomized controlled trials or controlled observational studies evaluated the impact of

injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

Injectable unfractionated heparin versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[88] In this trial by Santori and colleagues in 1994, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or venous foot pump prophylaxis. In patients who received injectable unfractionated heparin versus mechanical prophylaxis, the risk of deep vein thrombosis was significantly increased [RR 2.63 (1.36 to 5.25) NNH 5]. Subgroup analyses were not possible as this was the only trial available.

Oral vitamin K antagonists versus mechanical prophylaxis. Three randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[49,69,83] In patients who received oral vitamin K antagonists versus mechanical prophylaxis, the risk of deep vein thrombosis was not significantly different [RR 1.45 (0.75 to 2.82)] (Appendix Figure 121). A higher level of statistical heterogeneity was detected (I^2 = 58.5 percent) although publication bias could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery were not possible because no trials fit these criteria.

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

Asymptomatic deep vein thrombosis

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

Oral antiplatelet agents versus mechanical prophylaxis. One randomized controlled trial evaluated the impact or oral antiplatelet agent prophylaxis versus mechanical prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[75] This trial by Kennedy and colleagues in 2000 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus mechanical prophylaxis the odds of asymptomatic deep vein thrombosis were not significantly different [OR 1.45 (0.24 to 8.56)]. Subgroup analyses were not possible as only one trial was available.

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[64,89] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.70 (0.43 to 1.16)] (Appendix Figure 122). Statistical heterogeneity

and publication bias could not be evaluated because of too few strata. This result is the same when limiting the analysis to total hip replacement surgery. Subgroup analysis based on trials published 2001-present, hip fracture surgery and total knee replacement surgery were not possible because no trials fit these criteria.

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

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery, and both contributed two separate comparisons.[59,60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.97 (0.85 to 1.10)] (Appendix Figure 123). Statistical heterogeneity and publication bias were not detected ($I^2 = 0$ percent, Egger's p-value = 0.536). This is the same result obtained when limiting the analysis to trials published from 2001 to the present.

When limiting the original analysis to total hip replacement surgery one trial remained and provided two separate comparisons.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 1.08 (0.69 to 1.69)] (Appendix Figure 124). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery one trial that included two separate comparisons remained.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of asymptomatic deep vein thrombosis was not significantly different [RR 0.95 (0.83 to 1.09)] (Appendix Figure 125). Statistical heterogeneity could not be evaluated because of too few strata. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[77] This trial by Lassen and colleagues in 2007 evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of asymptomatic deep vein thrombosis was significantly decreased [RR 0.50 (0.28 to 0.88), NNT 8]. Subgroup analyses were not possible as only one trial was available.

Injectable low molecular weight heparin agents versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[91] This trial by Stone and colleagues in 1996 evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of asymptomatic deep vein thrombosis were not significantly different [OR 1.00 (0.06 to 16.45)]. Subgroup analyses were not possible as only one trial was available.

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

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

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

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

Symptomatic deep vein thrombosis

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

Oral antiplatelet agents versus mechanical prophylaxis. One randomized controlled trial evaluated the impact or oral antiplatelet prophylaxis versus mechanical prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[75] This trial by Kennedy and colleagues in 2000 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus mechanical prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.91 (0.37 to 9.75)]. Subgroup analyses were not possible as only one trial was available.

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Three randomized controlled trials evaluated the impact of injectable low molecular

weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[48,64,89] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.62 (0.22 to 1.75)] (Appendix Figure 126). Statistical heterogeneity was not detected (I^2 = 0 percent) but publication bias could not be evaluated because of too few strata. This result is the same when limiting the original analysis to total hip replacement surgery. Subgroup analysis based on trials published 2001-present, total knee replacement and hip fracture surgery were not possible because no trials fit these criteria.

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

Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had major orthopedic surgery.[67,90] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the odds of symptomatic deep vein thrombosis during the postdischarge period were not significantly different [OR 1.96 (0.20 to 19.02)] (Appendix Figure 127). Similar results were seen when evaluating total hip replacement surgery [OR 7.54 (0.47 to 122.28)][90] or total knee replacement surgery [OR 0.14 (0.003 to 6.90)][67] separately.

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on symptomatic deep vein thrombosis patients who had major orthopedic surgery.[51,57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.51 (0.22 to 1.21)] (Appendix Figure 128). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 3.5 percent, Egger's p-value = 0.878). This result is the same when limiting the original analysis trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were significantly decreased [OR 0.21 (0.06 to 0.78), NNT 322 to 416] (Appendix Figure 129). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery two trials remained.[51,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.01 (0.29 to 3.49)] (Appendix Figure 130). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to hip fracture surgery one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.99 (0.06 to 15.83)].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery, and all three provided two separate comparisons.[59,60,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.98 (0.34 to 2.87)] (Appendix Figure 131). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 47.5 percent, Egger's p-value = 0.476). This result is the same when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained and provided two separate comparisons.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 0.14 (0.02 to 1.03)] (Appendix Figure 132). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.[59,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of symptomatic deep vein thrombosis was not significantly different [RR 1.55 (0.58 to 4.20)] (Appendix Figure 133). A lower level of statistical heterogeneity was detected (I^2 = 35 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had total hip replacement surgery.[66] In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of symptomatic deep vein thrombosis during the postdischarge period were not significantly different [OR 0.51 (0.14 to 1.91)].

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Three randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[53,73,77] The trial by Hull and colleagues in 1993 provided two separate comparisons.[73] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.87 (0.61 to 1.24)] (Appendix Figure 134). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 28.4 percent, Egger's p-value = 0.376).

When limiting the original analysis to trials published from 2001-present one trial remained.[77] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.00 (0.06 to 16.09)]. This is the same result

obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery two trials remained.[53,73] The trial by Colwell and colleagues in 1999 contributed two separate comparisons.[53] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.87 (0.60 to 1.24)] (Appendix Figure 135). A higher level of statistical heterogeneity was detected (I^2 = 52.5 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[91,94] The trial by Stone and colleagues was excluded from the analysis because no events occurred in either group.[91] In remaining trial by Warwick and colleagues in 1998 patients who had total hip replacement surgery were evaluated. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 7.28 (0.14 to 367.07)]. Subgroup analyses were not possible because only one trial with events was available.

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

One randomized controlled trial evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitor prophylaxis on symptomatic deep vein thrombosis during the postdischarge period in patients who had total hip replacement surgery.[62] In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitor prophylaxis the odds of symptomatic deep vine thrombosis during the pos-discharge period were not significantly different [OR 1.50 (0.26 to 8.74)].

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. No randomized controlled trials or controlled observational studies evaluated the impact of oral vitamin K antagonist

prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Proximal deep vein thrombosis

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery.[81] In this trial by Lotke and colleagues in 1996, patients who had either total hip replacement or total knee replacement surgery were randomized to receive either aspirin or warfarin prophylaxis. In patients who received oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.78 (0.42 to 1.46)]. Subgroup analyses were not possible as this was the only trial available.

Oral antiplatelet agents versus mechanical prophylaxis. One randomized controlled trial by Haas and colleagues in 1990 evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery.[72] In this trial, patients who had either unilateral or bilateral total knee replacement surgery were randomized to receive either aspirin or intermittent pneumatic compression prophylaxis. Results were reported separately for unilateral and bilateral surgery, however no events occurred in the unilateral surgery group therefore only the bilateral surgery group remained. In these patients who received oral antiplatelet prophylaxis versus mechanical prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.57 (0.06 to 5.77)]. Subgroup analyses were not possible as this was the only trial available.

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Nine randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on proximal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.[48,54-56,67,79,86,89,98] In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.60 (0.38 to 0.93), NNT 14 to 50] (Appendix Figure 136). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 37 percent, Egger's p-value = 0.450).

Subgroup analysis based on trials published from 2001-present was not possible as all trials were published prior to 2001. When limiting the original analysis to total hip replacement surgery, six trials remained, with two trials including two separate comparisons.[48,54,56,79,86,89] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.58 (0.39 to 0.86), NNT 13 to 48] (Appendix Figure 137). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery, two trials remained.[55,67] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was significantly decreased [RR 0.32 (0.13 to 0.82), NNT 15 to 30] (Appendix Figure 138). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.[98] In this trial, in patients who received injectable low molecular

weight heparin agents versus injectable unfractionated heparin the risk of proximal deep vein thrombosis was not significantly different [RR 2.25 (0.95 to 5.61)].

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 2.24 (1.55 to 3.24), NNH 43 to 83] (Appendix Figure 139). A higher level of statistical heterogeneity was detected but publication bias was not detected (I^2 = 73.5 percent, Egger's p-value = 0.070). This is the same result obtained when limiting the analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery, two trials remained.[76,92] In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were not significantly different [OR 1.63 (0.95 to 2.80)] (Appendix Figure 140). Statistical heterogeneity was not evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 2.18 (1.04 to 4.57), NNH 45]. When limiting the original analysis to hip fracture surgery, one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 3.80 (1.92 to 7.50), NNH 38].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery with one trial including two separate comparisons.[66,87] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of proximal deep vein thrombosis was not significantly different [RR 0.91 (0.40 to 2.11)] (Appendix Figure 141). A higher statistical heterogeneity was detected (I^2 = 70.8 percent) and publication bias was not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained including two separate comparisons.[87] In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors the risk of proximal deep vein thrombosis was not significantly different [RR 0.58 (0.29 to 1.17)] (Appendix Figure 142). Statistical heterogeneity could not be evaluated because of too few studies. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.[66] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable or oral direct

thrombin inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 1.71 (1.13 to 2.59), NNH 151]. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

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

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared to enoxaparin in patients who had total hip or total knee replacement surgery.[58] Investigators reported a significant dose dependent decrease in the frequency of proximal deep vein thrombosis with increasing doses of dabigatran in both surgical groups ($p < 0.0001$) although direct comparison to enoxaparin was not made within this trial for this outcome.

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Six randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral vitamin K antagonists on proximal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.[68,70,73,74,77,78] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.63 (0.39 to 1.00)] (Appendix Figure 143). A higher level of statistical heterogeneity was detected but publication bias was not detected. (I^2 = 55.3 percent, Egger's p-value = 0.224).

When limiting the original analysis to trials published from 2001-present, two trials remained.[68,77] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.43 (0.05 to 4.11)] (Appendix Figure 144). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery, three trials remained with one trial including two separate comparisons.[70,73,74] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the odds of proximal deep vein thrombosis were not significantly different [OR 0.67 (0.42 to 1.08)] (Appendix Figure 145). A higher level of statistical heterogeneity was detected (I^2 = 55.3 percent). When limiting the original analysis to total knee replacement surgery, four trials remained.[68,73,77,78] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists the risk of proximal deep vein thrombosis was not significantly different [RR 0.63 (0.30 to 1.34)] (Appendix Figure 146). A higher level of statistical heterogeneity was detected (I^2 = 68.9 percent). Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.[91,94,95] In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the risk of proximal deep vein thrombosis was not significantly different [RR 0.65 (0.34 to 1.26)] (Appendix Figure 147). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias was not evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[95] In this trial, in patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.15 (0.02 to 1.05)]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.[91,94] In patients who received injectable low molecular weight heparin agents versus mechanical prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.71 (0.36 to 1.40)] (Appendix Figure 148). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

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

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on proximal deep vein thrombosis in patients who had major orthopedic surgery.[61,62] In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of proximal deep vein thrombosis were significantly increased [OR 4.74 (2.99 to 7.49), NNH 11] (Appendix Figure 149). A range for the NNH could not be calculated because the control event rate was the same in both groups. Statistical heterogeneity and publication bias were not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials published from 2001-present, total knee replacement surgery or hip fracture surgery could not be evaluated as no trials fit these criteria.

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

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. Three randomized controlled trials evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on proximal deep vein thrombosis in patients who had major orthopedic surgery.[49,69,83] In patients who received oral vitamin K antagonists versus mechanical prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.34 (0.16 to 0.73), NNT 11 to 31] (Appendix Figure 150). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias was not evaluated because of too few studies. This is the same result obtained when limiting the analysis to total hip replacement surgery. Subgroup analyses based on trials

published from 2001-present, total knee replacement surgery or hip fracture surgery could not be evaluated as no trials fit these criteria.

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

Distal deep vein thrombosis

Oral antiplatelet agents versus oral vitamin K antagonists. No randomized controlled trials or controlled observational studies evaluated the impact of oral antiplatelet agents versus oral vitamin K antagonists on distal deep vein thrombosis in patients who had major orthopedic surgery.

Oral antiplatelet agents versus mechanical prophylaxis. One randomized controlled trial by Haas and colleagues in 1990 evaluated the impact of oral antiplatelet agents versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[72] In this trial, patients who had total knee replacement surgery were randomized to receive either aspirin or intermittent pneumatic compression prophylaxis and results were reported separately for unilateral and bilateral surgery. In patients who received oral antiplatelet agents versus mechanical prophylaxis, the risk of distal deep vein thrombosis was significantly increased [RR 1.79 (1.15 to 2.79), NNH 4 to 6] (Appendix Figure 151). Statistical heterogeneity and publication bias could not be evaluated because there were too few studies. Subgroup analyses were not possible as this was the only trial available.

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Eight randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on distal deep vein thrombosis in patients who had major orthopedic surgery with two trials including two separate comparisons.[48,54-56,67,86,89,98] One trial was excluded from the analysis because no events occurred in the groups compared.[48] In patients who received injectable low molecular weight heparins versus injectable unfractionated heparin the risk of distal deep vein thrombosis was not significantly different [RR 0.95 (0.74 to 1.23)] (Appendix Figure 152). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.544).

Subgroup analysis based on trials published from 2001-present was not possible because no trials fit this criterion. When limiting the original analysis to total hip replacement surgery, five trials remained, with two trials including two separate comparisons.[48,54,56,86,89] One trial was excluded from the analysis because no events occurred in the groups compared.[48] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of distal deep vein thrombosis was not significantly different [RR 1.03 (0.58 to 1.83)] (Appendix Figure 153). Statistical heterogeneity was not detected (I^2 = 0 percent).When limiting the original analysis to total knee replacement surgery, two trials remained.[55,67] In patients who received injectable low molecular weight heparin versus injectable unfractionated heparin, the risk of distal deep vein thrombosis was not significantly different [RR 0.93 (0.69 to 1.24)] (Appendix Figure 154). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to hip fracture surgery, one trial remained.[98] In this trial, in patients who received injectable low molecular weight heparin versus injectable

unfractionated heparin, the odds of distal deep vein thrombosis were not significantly different [OR 1.86 (0.19 to 18.65)].

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on distal deep vein thrombosis in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparins versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.08 (1.72 to 2.52), NNH 10 to 31] (Appendix Figure 155). Statistical heterogeneity and publication bias were not detected ($I^2 = 0$ percent, Egger's p-value = 0.418). This is the same result obtained when limiting the analysis to trials published from 2001-present since all four trials fit this criterion.

When limiting the original analysis to total hip replacement surgery, two trials remained.[76,92] In patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the odds of distal deep vein thrombosis were significantly increased [OR 1.90 (1.42 to 2.56), NNH 30 to 40] (Appendix Figure 156). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery, one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.27 (1.57 to 3.28), NNH 8]. When limiting the original analysis to hip fracture surgery, one trial remained.[57] In this trial in patients who received injectable low molecular weight heparin versus injectable or oral factor Xa inhibitors, the risk of distal deep vein thrombosis was significantly increased [RR 2.24 (1.59 to 3.17), NNH 12].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. One randomized controlled trial by Ginsberg and colleagues in 1990, including two separate comparisons, evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on distal deep vein thrombosis in patients who had major orthopedic surgery and included two separate comparisons.[87] In this trial, patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg. In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors, the risk of distal deep vein thrombosis was significantly decreased [RR 0.79 (0.67 to 0.93), NNT 16 to 18] (Appendix Figure 157). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses were not possible as this was the only trial available.

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared to enoxaparin in patients who had total hip or total knee replacement surgery.[58] Investigators reported a significant dose dependent decrease in the frequency of distal deep vein thrombosis with increasing doses of dabigatran in both surgical groups ($p < 0.0001$) although direct comparison to enoxaparin was not made within this trial for this outcome.

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on distal deep vein thrombosis in patients who had major orthopedic surgery.[68,70] In patients who received injectable low molecular weight heparins versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.56 (0.43 to 0.73), NNT 6 to 10] (Appendix Figure 158). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[68] In this trial, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.60 (0.44 to 0.81), NNT 6]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.[70] In this trial, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonists, the risk of distal deep vein thrombosis was significantly decreased [RR 0.48 (0.30 to 0.78), NNT 9]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[91,94,95] One trial was excluded from the analysis because no events occurred in the groups compared.[91] In patients who received injectable low molecular weight heparins versus mechanical prophylaxis, the risk of distal deep vein thrombosis was not significantly different [RR 1.00 (0.77 to 1.29)] (Appendix Figure 159). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[95] In this trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis, the risk of distal deep vein thrombosis was not significantly different [RR 1.01 (0.77 to 1.31)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, two trials remained.[91,94] One trial was excluded from the analysis because no events occurred in the groups compared leaving one trial for the analysis.[91] In the remaining trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis, the odds of distal deep vein thrombosis were not significantly different [OR 0.84 (0.28 to 2.55)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

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

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial by Paiement and colleagues in 1987 evaluated the impact of oral vitamin K antagonists versus mechanical prophylaxis on distal deep vein thrombosis in patients who had major orthopedic surgery.[83] In this trial, patients who had total hip replacement surgery were randomized to receive either warfarin or intermittent pneumatic compression prophylaxis. In patients who received oral vitamin K antagonists versus mechanical prophylaxis, the odds of distal deep vein thrombosis were not significantly different [OR 3.30 (0.91 to 11.91)]. Subgroup analyses were not possible as this was the only trial available.

Major bleeding

Oral antiplatelet agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of oral antiplatelet agent prophylaxis versus oral vitamin k antagonist prophylaxis on major bleeding in patients who had major orthopedic surgery.[125] This trial by Powers and colleagues in 1989 evaluated patients who had hip fracture surgery. In patients who received oral antiplatelet agent prophylaxis versus oral vitamin K antagonist prophylaxis the risk of major bleeding was not significantly different [RR 0.20 (0.03 to 1.23)]. Subgroup analyses were not possible as only one trial was available.

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on major bleeding in patients who had major orthopedic surgery.[54,55,64,79,82,86,90] Two trials provided two separate comparisons.[54,82] The trial by Eriksson in 1991 could not be pooled as no events occurred in either group.[64] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were significantly decreased [OR 0.57 (0.37 to 0.88), NNT 41] (Appendix Figure 160). A range for the number needed to treat could not be calculated since the lowest control events rate was zero. A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 37.1 percent, Egger's p-value = 0.608).

When limiting the original analysis to trials published from 2001-present, one trial remained.[90] In this trial, in patients who received injectable low molecular weight heparin

prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were not significantly different [OR 7.54 (0.47 to 122.28)]. When limiting the original analysis to total hip replacement surgery six trials remained.[54,64,79,82,86,90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were significantly decreased [OR 0.54 (0.34 to 0.85), NNT 38] (Appendix Figure 161). A range for the number needed to treat could not be calculated since the lowest control events rate was zero. A lower level of statistical heterogeneity was detected (I^2 = 43.5 percent). When limiting the original analysis to total knee replacement surgery one trial remained.[55] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of major bleeding were not significantly different [OR 0.99 (0.20 to 4.93)]. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this population.

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on major bleeding in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.65 (0.48 to 0.89), NNT 74 to 145] (Appendix Figure 162). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 56.6 percent, Egger's p-value = 0.347). This is the same result obtained when limiting the analysis to trials published from 2001 to the present.

When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.64 (0.44 to 0.94), NNT 72 to 141] (Appendix Figure 163). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were significantly decreased [OR 0.19 (0.06 to 0.58), NNT 62]. When limiting the original analysis to hip fracture surgery one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding were not significantly different [OR 1.04 (0.54 to 2.00)].

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

One controlled observational study evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on bleeding in patients who had major orthopedic surgery.[139] Although not reported as major bleeding, the definition used in this study is similar to those used in the trials evaluated above. This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received either an injectable low molecular weight heparin (enoxaparin or dalteparin) or fondaparinux prophylaxis. Bleeding was not significantly different in patients who received

injectable low molecular weight heparin versus fondaparinux prophylaxis (1.5 percent versus 1.5 percent, p = 0.970).

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding in patients who had major orthopedic surgery.[59,60,66,87] The trials by Erikson and colleagues in 2007 and the trial by Ginsberg and colleagues in 2009 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.12 (0.80 to 1.57)] (Appendix Figure 164). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.175).

When limiting the original analysis to trials published from 2001-present, three trials remained each including two separate comparisons.[59,60,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.17 (0.79 to 1.75)] (Appendix Figure 165). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total hip replacement surgery two trials remained with the trial by Eriksson and colleagues in 2007 including two separate comparisons.[60,66] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 0.97 (0.64 to 1.48)] (Appendix Figure 166). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.[59,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding was not significantly different [RR 1.46 (0.82 to 2.59)] (Appendix Figure 167). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

In the dose finding trial by Eriksson and colleagues in 2005 four doses of dabigatran were compared to enoxaparin in patients who had total hip or total knee replacement surgery.[58] Investigators reported that major bleeding episodes were significantly higher in the dabigatran 150mg twice daily, dabigatran 225mg twice daily, and the dabigatran 300mg daily groups compared to the dabigatran 50mg twice daily group although results were not reported. When compared to enoxaparin, the dabigatran 50mg twice daily group had significantly less major bleeding episodes (0.3 percent versus 2.0 percent, p=0.047). However, the occurrence of major bleeding was not significantly different when comparing the other dabigatran groups to enoxaparin. Authors suggested a nonsignificant trend towards increased major bleeding with dabigatran 150mg twice daily, 225mg twice daily, and 300mg daily compared to enoxaparin.

One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding during the postdischarge time period in patients who had total knee replacement surgery.[87] In this trial patients who had total knee replacement surgery were

randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg daily. In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding during the postdischarge period was not significantly different [RR 0.51 (0.06 to 4.58)] (Appendix Figure 168).

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Seven randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on major bleeding in patients who had major orthopedic surgery.[53,68,70,73,74,77,78] The trial by Hull and colleagues in 1993 provided two separate comparisons and the trial by Lassen and colleagues in 2007 was excluded from the analysis because no events occurred in either group compared. Another trial by Hull and colleagues in 2000 included two separate comparisons but was not included in the pooled analysis because major bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.[74] The six remaining trials were pooled, and in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of major bleeding was significantly increased [OR 1.92 (1.27 to 2.91), NNH 57 to 220] (Appendix Figure 169). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.661).

The trial by Hull and colleagues in 2000 that was excluded from the pooled analysis was evaluated separately. In this trial, patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of major bleeding was not significantly different on days 0-1 [RR 1.51 (0.92 to 2.48)] (Appendix Figure 170) or on days 2-8 [RR 3.41 (0.77 to 15.18)] (Appendix Figure 171).

When limiting the original pooled analysis of six trials to trials published from 2001-present two trials remained.[68,77] The trial by Lassen and colleagues in 2007 was excluded from the analysis because no events occurred in either group.[77] In the remaining trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were not significantly different [OR 2.26 (0.75 to 6.83)]. When limiting the original analysis to total hip replacement surgery three trials remained.[53,70,73] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were significantly increased [OR 1.91 (1.11 to 3.29), NNH 58 to 220] (Appendix Figure 172). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery four trials remained.[68,73,77,78] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding were significantly increased [OR 1.93 (1.01 to 3.67), NNH 56] (Appendix Figure 173). A range for the number needed to harm could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected (I^2 = 0 percent). No trials evaluated patients with hip fracture surgery.

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. No randomized controlled trials or controlled observational studies evaluated the impact of

injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

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

Injectable unfractionated heparin versus injectable or oral factor Xa inhibitors. One controlled observational study evaluated the impact of injectable unfractionated heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on bleeding in patients who had major orthopedic surgery.[139] Although not reported as major bleeding, the definition used in this study is similar to those used in the trials evaluated above. This study evaluated patients who had total hip replacement, total knee replacement, or hip fracture surgery and received injectable unfractionated heparin or fondaparinux prophylaxis. Bleeding was significantly increased in patients who received unfractionated heparin versus fondaparinux prophylaxis [OR 1.27 (1.06 to 1.52), NNH 253].

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin k antagonist prophylaxis versus mechanical prophylaxis on major bleeding in patients undergoing major orthopedic surgery although no events occurred therefore the risk of major bleeding could not be evaluated.[83]

Major bleeding leading to reoperation

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery although no events occurred therefore the risk of major bleeding leading to reoperation could not be evaluated.[64]

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. Four randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.[57,76,92,99] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.67 (0.28 to 1.61)] (Appendix Figure 174). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.855). This is the same result as limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery two trials remained.[76,92] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation was not significantly different [OR 0.72 (0.23 to 2.23)] (Appendix Figure 175). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one trial remained.[99] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.51 (0.05 to 4.94)].When limiting the original analysis to hip fracture surgery one trial remained.[57] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 0.66 (0.11 to 3.82)].

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.[59,60,87] All three trials provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.27 (0.43 to 3.75)] (Appendix Figure 176). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.614). This is the same result obtained when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained including two separate comparisons.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.21 (0.29 to 5.08)] (Appendix Figure 177). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.[59,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 1.36 (0.27 to 7.03)] (Appendix Figure 178). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Two randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery.[68,70] One trial was excluded from the analysis because no events occurred in the groups compared.[68] The remaining trial by Francis and colleagues in 1997 evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 7.61 (0.15 to 383.70)]. Subgroup analyses were not possible as only one trial had events in the groups compared.

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

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on major bleeding leading to reoperation in patients who had major orthopedic surgery.[61,62] One trial was excluded from the analysis because no events occurred in the groups compared.[62] In the remaining trial by Eriksson and colleagues in 1996, patients who had total hip replacement surgery were evaluated. In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors the odds of major bleeding leading to reoperation were not significantly different [OR 0.51 (0.10 to 2.55)]. Subgroup analyses were not possible since only one trial had events in the groups compared.

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on major bleeding leading to reoperation in patients who had major orthopedic surgery although no events occurred therefore the risk of major bleeding leading to reoperation could not be calculated.[69]

Minor bleeding

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Five randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on minor bleeding in patients who had major orthopedic surgery.[54,55,79,86,90] The trial by Colwell and colleagues in 1994 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of minor bleeding was not significantly different [RR 0.90 (0.63 to 1.28)] (Appendix Figure 179). A lower level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 9.9 percent, Egger's p-value = 0.608).

When limiting the original analysis to trials published from 2001-present, one trial remained.[90] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of minor bleeding was not significantly different [OR 0.25 (0.03 to 2.16)]. When limiting the original analysis to total hip replacement surgery, four trials remained.[54,79,86,90] The trial by Colwell and colleagues in 1994 provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the odds of minor bleeding were not significantly different [OR 0.92 (0.57 to 1.51)] (Appendix Figure 180). A lower level of statistical heterogeneity was detected (I^2 = 31.4 percent). When limiting the original analysis to total knee replacement surgery one trial remained.[55] In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis the risk of major bleeding leading to reoperation was not significantly different [RR 0.87 (0.60 to 1.25)]. Subgroup analyses based on hip fracture surgery were not possible as no trials evaluated these surgical populations.

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. One randomized controlled trial evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on minor bleeding in patients who had major orthopedic surgery.[57] This trial by Eriksson and colleagues in 2001 evaluated patients who had hip fracture surgery. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis the odds of minor bleeding were significantly decreased [OR 0.52 (0.30 to 0.91), NNT 54]. As such, the same results occurred when trials were limited to the years 2001 to the present. Subgroup analyses were not possible as only one trial was available.

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on minor bleeding in patients who had major orthopedic surgery.[59,60,87] All three trials provided two separate comparisons. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.07 (0.89 to 1.29)] (Appendix Figure 181). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.132). This is the same result obtained when limiting the original analysis to trials published from 2001-present.

When limiting the original analysis to total hip replacement surgery one trial remained including two separate comparisons.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.04 (0.79 to 1.37)] (Appendix Figure 182). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery two trials that included two separate comparisons remained.[59,87] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding was not significantly different [RR 1.10 (0.86 to 1.40)] (Appendix Figure 183). Statistical heterogeneity was not detected (I^2 = 0 percent). Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

One randomized controlled trial including two separate comparisons evaluated the impact of injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis on minor bleeding during the postdischarge time period in patients who had total knee replacement surgery.[87] In this trial patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg daily. In patients who received injectable low molecular weight heparin versus injectable or oral direct thrombin inhibitor prophylaxis the risk of minor bleeding during the postdischarge period was not significantly different [RR 0.54 (0.15 to 1.95)] (Appendix Figure 184).

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Eight randomized controlled trials evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on minor bleeding in patients who had major orthopedic surgery. [53,68,70,73,74,77,78] The trial by Hull and colleagues in 1993 provided two separate comparisons.[73] The trial Hull and colleagues in 2000 including two separate comparisons but was excluded from the pooled analysis because minor bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.[74] The remaining seven trials were pooled and in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was significantly increased [RR 1.23 (1.06 to 1.43), NNH 18 to 218] (Appendix Figure 185). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.311).

The trial by Hull and colleagues in 2000 that was excluded from the pooled analyses was evaluated separately.[73] In this trial patients who had total hip replacement surgery were

randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different on days 0-1 [RR 1.49 (0.30 to 7.37)] (Appendix Figure 186) or on days 2-8 [RR 0.87 (0.37 to 2.06)] (Appendix Figure 187).

When limiting the original pooled analysis of seven trials to trials published from 2001-present two trials remained.[68,77] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.25 (0.85 to 1.83)] (Appendix Figure 188). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total hip replacement surgery three trials remained.[53,70,73] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.26 (0.85 to 1.86)] (Appendix Figure 189). A lower level of statistical heterogeneity was detected (I^2 = 27.8 percent). When limiting the original analysis to total knee replacement surgery four trials remained.[68,73,77,78] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the risk of minor bleeding was not significantly different [RR 1.17 (0.95 to 1.43)] (Appendix Figure 190). Statistical heterogeneity was not detected (I^2 = 0 percent). No trials evaluated patients with hip fracture surgery.

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

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

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

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

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

Oral vitamin K antagonists versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on minor bleeding in patients who had major orthopedic surgery.[69,83] In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist

prophylaxis the odds of minor bleeding were not significantly different [OR 0.80 (0.26 to 2.41)] (Appendix Figure 191). Statistical heterogeneity and publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the analysis to trials limited to total hip replacement surgery. Subgroup analyses based on trials published 2001-present, total knee replacement and hip fracture surgery were not possible as no trials fit these criteria.

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

Surgical site bleeding

Oral antiplatelet agents versus oral vitamin K antagonists. One controlled observational study evaluated the impact of oral antiplatelet prophylaxis versus oral vitamin K antagonist prophylaxis on surgical site bleeding in patients who had major orthopedic surgery.[140] This study evaluated patients who had total knee replacement surgery and who received either aspirin or warfarin prophylaxis.[140] The odds of surgical site bleeding for patients who received warfarin versus aspirin prophylaxis were not significantly different [AOR 0.97 (0.65 to 1.47)].

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus injectable unfractionated heparin on surgical site bleeding in patients who had major orthopedic surgery with one trial including two separate comparisons.[54,55,90] In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of surgical site bleeding were not significantly different [OR 0.92 (0.46 to 1.82)] (Appendix Figure 192). A lower level of statistical heterogeneity and the presence of publication bias were detected (I^2 = 41.4 percent, Egger's p-value = 0.021).

When limiting the original analysis to trials published from 2001-present, one trial remained.[90] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of surgical site bleeding was not significantly different [RR 0.75 (0.20 to 2.86)]. When limiting the original analysis to total hip replacement surgery, two trials remained with one trial including two separate comparisons.[54,90] In patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the risk of surgical site bleeding was not significantly different [RR 0.63 (0.26 to 1.55)] (Appendix Figure 193). A lower level of statistical heterogeneity was detected (I^2 = 3.1 percent). When limiting the original analysis to total knee replacement surgery, one trial remained.[55] In this trial, in patients who received injectable low molecular weight heparin agents versus injectable unfractionated heparin, the odds of surgical site bleeding were not significantly different [OR 1.78 (0.61 to 5.14)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. One randomized controlled trial by Lassen and colleagues in 2002 evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors on surgical site bleeding in patients who had major orthopedic surgery.[76] In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin or fondaparinux prophylaxis. In patients who received injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors, the odds of surgical site bleeding were not significantly different [OR 0.72 (0.45 to 1.17)]. Subgroup analyses were not possible as this was the only trial available.

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. One randomized controlled trial by Ginsberg and colleagues in 2009 evaluated the impact of injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors on surgical site bleeding in patients who had major orthopedic surgery and included two separate comparisons.[87] In this trial, patients who had total knee replacement surgery were randomized to receive either enoxaparin, dabigatran 150mg or dabigatran 220mg. In patients who received injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors, the risk of surgical site bleeding was significantly increased [RR 4.35 (1.51 to 12.54), NNH 100 to 105] (Appendix Figure 194). Subgroup analyses were not possible as this was the only trial available.

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on surgical site bleeding in patients who had major orthopedic surgery.[68,70] In patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were significantly increased [OR 2.63 (1.31 to 5.28), NNH 23 to 64] (Appendix Figure 195). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

When limiting the original analysis to trials published from 2001-present, one trial remained.[68] In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were not significantly different [OR 2.05 (0.80 to 5.29)]. This is the same result obtained when limiting the analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement surgery, one trial remained.[70] In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of surgical site bleeding were significantly increased [OR 3.53 (1.27 to 9.84), NNH 42]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this surgical population.

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

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on major surgical site bleeding in patients who had major orthopedic surgery.[53,73,74] The trial by Hull and colleagues in 2000 was excluded from the pooled analysis because major surgical site bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.[74] The remaining two trials were pooled and in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of major surgical site bleeding were significantly increased [OR 2.51 (1.38 to 4.54), NNH

70 to 224] (Appendix Figure 196). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

The trial by Hull and colleagues in 2000 that was excluded from the pooled analysis was evaluated separately.[74] In this trial patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. In patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the risk of major surgical site bleeding was significantly increased on days 0 to 1 [RR 1.72 (1.02 to 2.92), NNH 47] (Appendix Figure 197) but was not significantly different on days 2 to 8 [RR 2.72 (0.59 to 12.44)] (Appendix Figure 198). A range for the number needed to harm for major surgical site bleeding on days 0-1 could not be calculated because the control events rate was the same in both groups.

When limiting the original pooled analysis of two trials to total hip replacement surgery, one trial remained.[53] In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of major surgical site bleeding were significantly increased [OR 2.56 (1.04 to 6.30), NNH 216]. Subgroup analyses based on trials published from 2001-present, total knee replacement or hip fracture surgery were not possible because no trials fit these criteria. The trial by Hull and colleagues in 1993 evaluated both toal hip and knee replacement surgery although did not report results separately. Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin agents versus oral vitamin K antagonists on minor surgical site bleeding in patients who had major orthopedic surgery.[53,73,74] The trial by Hull and colleagues in 2000 was excluded from the pooled analysis because minor surgical site bleeding was reported at two postoperative time periods; days 0-1 and days 2-8.[74] The two remaining trials were pooled and in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of minor surgical site bleeding were not significantly different [OR 1.34 (0.91 to 1.97)] (Appendix Figure 199). Statistical heterogeneity and publication bias could not be evaluated because of too few studies.

The trial by Hull and colleagues in 2000 was excluded from the pooled analysis and was evaluated separately.[74] In this trial patients who had total hip replacement surgery were randomized to receive dalteparin initiated preoperatively, dalteparin initiated postoperatively or warfarin prophylaxis. No events occurred in the comparison of dalteparin initiated preoperatively versus warfarin. In the remaining comparison, in patients who received injectable low molecular weight heparin versus oral vitamin K antagonist prophylaxis the odds of minor surgical site bleeding were not significantly different on days 0 to 1 [OR 7.42 (0.15 to 373.92)] or on days two to eight [OR 7.43 (0.46 to 119.03)].

When limiting the original pooled analysis of two trials to total hip replacement surgery, one trial remained.[53] In this trial, in patients who received injectable low molecular weight heparin agents versus oral vitamin K antagonists, the odds of minor surgical site bleeding were not significantly different [OR 1.37 (0.93 to 2.02)]. Subgroup analyses based on trials published from 2001-present, total knee replacement or hip fracture surgery were not possible because no trials fit these criteria. Subgroup analyses based on age, gender and ethnicity were not possible because no randomized controlled trials reported data based on these subgroups.

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

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. One randomized controlled trial by Eriksson and colleagues in 1996 evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on surgical site bleeding in patients who had major orthopedic surgery.[61] In this trial, patients who had total hip replacement surgery were randomized to receive either unfractionated heparin or desirudin. In patients who received injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors, the odds of surgical site bleeding were not significantly different [OR 0.87 (0.31 to 2.43)]. Subgroup analyses were not possible as this was the only trial available.

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

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

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

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

Bleeding leading to transfusion

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. No randomized controlled trials or controlled observational studies evaluated the

impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis in patients who had major orthopedic surgery on this outcome.

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

Injectable low molecular weight heparin agents versus injectable or oral direct thrombin inhibitors. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery and each trial included two separate comparisons.[59,60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not significantly different [RR 1.00 (0.59 to 1.69)] (Appendix Figure 200). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.827). This is the same result obtained when limiting the original analysis to trials published from 2001-present. When limiting the original analysis to total hip replacement surgery, one trial which included two separate comparisons remained.[60] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not significantly different [RR 1.19 (0.46 to 3.10)] (Appendix Figure 201). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery, one trial which included two separate comparisons remained.[59] In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral direct thrombin inhibitor prophylaxis, the risk of bleeding leading to transfusion was not statistically significant [RR 0.71 (0.26 to 1.98)] (Appendix Figure 202). Statistical heterogeneity could not be evaluated because of too few strata. No trials evaluated patients who had hip fracture surgery.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.[70] This trial by Francis and colleagues in 1997, evaluated patients who had total hip replacement surgery. In this trial, in patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis the odds of bleeding leading to transfusion were not significantly different [OR 1.71 (0.42 to 6.90)]. Subgroup analyses were not possible because only one trial was available.

Injectable low molecular weight heparin agents versus mechanical prophylaxis. No randomized controlled trials or controlled observational studies evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.

Injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors. No randomized controlled trials or controlled observational studies evaluated the impact of injectable unfractionated heparin versus injectable or oral direct thrombin inhibitors on bleeding leading to transfusion in patients who had major orthopedic surgery.

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

Injectable unfractionated heparin versus mechanical prophylaxis. No randomized controlled trials or controlled observational studies evaluated the impact injectable unfractionated heparin prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion in patients who had major orthopedic surgery.

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trial evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on bleeding leading to transfusion although no events occurred in the groups compared therefore the risk could not be calculated.[69]

Heparin induced thrombocytopenia

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Three randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on heparin-induced thrombocytopenia in patients who had major orthopedic surgery.[54,79,90] One trial by Colwell and colleagues included two separate comparisons.[54] One trial was excluded from the analysis because no events occurred in the groups compared.[90] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the odds of heparin induced thrombocytopenia was significantly decreased [OR 0.12 (0.03 to 0.43), NNT 34 to 202] (Appendix Figure 203). Statistical heterogeneity was not detected (I^2 = 0 percent) and publication bias could not be evaluated because of too few strata. This is the same result obtained when limiting the original analysis to total hip replacement as all three trials were conducted in this surgical population. No trials evaluated total knee replacement or hip fracture surgery. When limiting the original analysis to trials published from 2001-present, one trial remained although no events occurred in the groups compared.[90]

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

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

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. One randomized controlled trial evaluated the impact of injectable low molecular weight prophylaxis versus oral vitamin K antagonist prophylaxis on heparin-induced thrombocytopenia in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of heparin-induced thrombocytopenia could not be calculated.[53]

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

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

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

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

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

Discomfort

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

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

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

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

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

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. One randomized controlled trial by Warwick and colleagues in 1998 evaluated the impact of injectable low molecular weight heparin versus mechanical prophylaxis on discomfort in patients who had major orthopedic surgery.[94] In this trial, patients who had total hip replacement surgery were randomized to receive either enoxaparin or venous foot pump prophylaxis. Although the discomfort was defined differently in each arm, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis the risk of discomfort was significantly decreased [RR 0.49 (0.29 to 0.82), NNT 7].

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

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

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

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

Readmission

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

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

Injectable low molecular weight heparin agents versus injectable unfractionated heparin. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis on readmission in patients who had major orthopedic surgery.[54,90] One trial by Colwell and colleagues included two separate comparisons.[54] In patients who received injectable low molecular weight heparin prophylaxis versus injectable unfractionated heparin prophylaxis, the risk of readmission was not significantly different [RR 0.82 (0.20 to 3.38)] (Appendix Figure 204). A lower level of statistical heterogeneity was detected (I^2 = 14.1 percent) and publication bias could not be evaluated because of too few studies. This is the same results obtained when limiting the original analysis to total hip replacement as both trials were conducted in this surgical population. No trials evaluated total knee replacement or hip fracture surgery. When limiting the original analysis to trials published from 2001-present, one trial remained.[90] In this trial, in patients who received injectable low molecular weight heparin versus injectable unfractionated heparin prophylaxis, the odds of readmission were not significantly different [OR 7.54 (0.47 to 122.23)].

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. No randomized controlled trials or controlled observational studies evaluated the

impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis in patients who had major orthopedic surgery on this outcome.

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

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

Injectable low molecular weight heparin agents versus mechanical prophylaxis. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis on readmission in patients who had major orthopedic surgery.[94,95] In patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of readmission were not significantly different [OR 0.83 (0.22 to 3.11)] (Appendix Figure 205). Statistical heterogeneity and publication bias could not be evaluated because of too few strata.

When limiting the original analysis to trials published from 2001-present one trial by Warwick and colleagues remained.[95] In this trial in patients who received injectable low molecular weight heparin prophylaxis versus mechanical prophylaxis the odds of readmission were not significantly different [OR 0.78 (0.17 to 3.50)]. This is the same result obtained when limiting the original analysis to total knee replacement surgery. When limiting the original analysis to total hip replacement, one trial remained.[94] In this trial, in patients who received injectable low molecular weight heparin versus mechanical prophylaxis the odds of readmission were not significantly different [OR 1.03 (0.06 to 16.52)]. No trials evaluated hip fracture surgery.

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

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

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

Injectable unfractionated heparin versus mechanical prophylaxis. No randomized controlled trials or controlled observational studies evaluated the impact of injectable

unfractionated heparin versus mechanical prophylaxis in patients who had major orthopedic surgery on this outcome.

Oral vitamin K antagonists versus mechanical prophylaxis. One randomized controlled trials evaluated the impact of oral vitamin K antagonist prophylaxis versus mechanical prophylaxis on readmission in patients who had major orthopedic surgery.[49] This trial evaluated patients who had total hip replacement surgery. In patients who received oral vitamin K antagonist prophylaxis versus mechanical prophylaxis, the odds of readmission were not significantly different [OR 0.15 (0.003 to 7.58)]. Subgroup analyses were not possible because only one trial was available.

Reoperation

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

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

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

Injectable low molecular weight heparin agents versus injectable or oral factor Xa inhibitors. One randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis on reoperation in patients who had major orthopedic surgery.[51] This trial by Bonneaux and colleagues in 2006 evaluated patients who had total knee replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus injectable or oral factor Xa inhibitor prophylaxis, the risk of reoperation was not significantly different [RR 0.25 (0.04 to 1.63)]. Subgroup analyses were not possible since this was the only trial available.

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

Injectable low molecular weight heparin agents versus oral vitamin K antagonists. Two randomized controlled trials evaluated the impact of injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis on reoperation in patients who had major orthopedic surgery.[68,70] One trial was excluded from the analysis because no events

occurred, leaving the trial by Francis and colleagues in 1997.[70] This trial evaluated patients who had total hip replacement surgery. In patients who received injectable low molecular weight heparin prophylaxis versus oral vitamin K antagonist prophylaxis, the risk of reoperation was not significantly different [RR 0.85 (0.59 to 1.22)]. Subgroup analyses were not possible because only one trial with events was available.

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

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

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

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

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

Table 11. Significant differences between comparative groups for outcomes in base case and subgroup analyses in key quesiont five.

	ATP vs. VKA	ATP vs. Mech	LMWH vs. UFH	LMWH vs. FXA	LMWH vs. DTI	LMWH vs. VKA	LMWH vs. Mech	UFH vs. DTI	UFH vs. FXA	UFH vs. Mech	VKA vs. Mech
Final health outcomes											
Base Case	↑ Death* ↑ fPE*		↓ PE	↑ Death*					↑ Death*		
2001-Present	↑ Death* ↑ fPE*			↑ Death*					↑ Death*		
THR			↓ PE ↓ nfPE	↓ sVTE ↓ nfPE							
TKR											
HFS			↑ PE ↑ nfPE								
Intermediate health outcomes											
Base Case		↑ DVT ↑ dDVT	↓ DVT ↓ pDVT	↑ DVT ↑ pDVT ↑ dDVT	↑ DVT ↓ dDVT	↓ DVT ↓ asDVT ↓ pDVT ↓ dDVT		↑ DVT ↑p DVT		↑ DVT	↓ pDVT
2001-Present				↑ DVT ↑ pDVT ↑ dDVT	↓ dDVT	↓ DVT ↓ asDVT ↓ dDVT					
THR			↓ DVT ↓ pDVT	↑ DVT ↑ dDVT ↓ sDVT	↑ pDVT	↓ DVT ↓ dDVT		↑ DVT ↑ pDVT			↓ pDVT
TKR		↑ DVT ↑ dDVT	↓ DVT ↓ pDVT	↑ DVT ↑ pDVT ↑ dDVT	↓ dDVT	↓ DVT ↓ asDVT ↓ dDVT					
HFS			↑ DVT	↑ DVT ↑ pDVT ↑ dDVT							

	ATP vs. VKA	ATP vs. Mech	LMWH vs. UFH	LMWH vs. FXA	LMWH vs. DTI	LMWH vs. VKA	LMWH vs. Mech	UFH vs. DTI	UFH vs. FXA	UFH vs. Mech	VKA vs. Mech
Adverse outcomes											
Base Case			↓ MJB ↓ HIT	↓ MJB ↓ MNB	↑ SSB	↑ MJB ↑ MNB ↑ SSB	↓ DC		↑ MJB*		
2001-Present				↓ MJB ↓ MNB	↑ SSB				↑ MJB*		
THR			↓ MJB ↓ HIT	↓ MJB		↑ MJB ↑ SSB	↓ DC				
TKR				↓ MJB	↑ SSB	↑ MJB					
HFS				↓ MNB							

*based on observational data
↓ denotes significantly fewer occurrences in group A vs. group B
↑ denotes significantly more occurrences in group A than group B

Abbreviations: asDVT=asymptomatic deep vein thrombosis; ATP=antiplatelet; DC=discomfort; dDVT=distal deep vein thrombosis; DTI=direct thrombin inhibitor; DVT =deep venous thrombosis ; fPE=fatal pulmonary embolism; FXA = factor Xa inhibitors; HFS=hip fracture surgery; HIT=heparin induced thrombocytopenia; LMWH =low molecular weight heparin; Mech = mechanical prophylaxis; MJB = major bleeding; MNB = minor bleeding; nf PE=nonfatal pulmonary embolism; OBS =data derived from a controlled observational study; pDVT=proximal deep vein thrombosis; PE=pulmonary embolism; sDVT=symptomatic deep vein thrombosis; SSB =surgical site bleeding; THR=total hip replacement; TKR=total knee replacement; UFH =unfractionated heparin; VKA =vitamin K antagonist; vs=versus

Table 12. Summary of results for key question 5*

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
Symptomatic objectively confirmed VTE				
Antiplatelet versus oral VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	1 RCT	No	OR 0.13 (0.01 to 2.15)	NA
	1 RCT	No	One RCT evaluated this outcome during the post-discharge period and showed an OR 7.54 (0.47 to 122.28)	NA
LMWH versus factor Xa inhibitors	4 RCTs	Yes	OR 0.71 (0.49 to 1.04)	48.6
▪ Limited to 2001-present	4 RCTs	Yes	OR 0.71 (0.49 to 1.04)	48.6
▪ Limited to THR	2 RCTs	Yes	OR 0.54 (0.33 to 0.89)	NA
▪ Limited to TKR	1 RCT	No	OR 1.97 (0.71 to 5.45)	NA
▪ Limited to HFS	1 RCT	No	OR 0.75 (0.37 to 1.55)	NA
LMWH versus DTI	0	---	---	---
LMWH versus VKA	2 RCTs	Yes	OR 1.00 (0.69 to 1.46);	NA
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed an OR 2.24 (0.65 to 7.79)	NA
▪ Limited to THR	1 RCT	No	OR 0.97 (0.66 to 1.41)	NA
▪ Limited to TKR	1 RCT	No	OR 2.71 (0.38 to 19.35)	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Major venous thromboembolism				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	0	---	---	---
LMWH versus factor Xa inhibitors	0	---	---	---
LMWH versus DTI	3 RCTs	Yes	RR 1.26 (0.98 to 1.62)	0
▪ Limited to 2001-present	2 RCTs	Yes	RR 1.08 (0.78 to 1.50)	0

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to THR	2 RCTs	Yes	RR 1.28 (0.94 to 1.76)	18.6
▪ Limited to TKR	1 RCT	No	RR 1.11 (0.63 to 1.96)	NA
LMWH versus VKA	0	---	---	---
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Pulmonary embolism				
Antiplatelet versus VKA	1 RCT	No	OR 7.28 (0.14 to 366.83)	NA
Antiplatelet versus mechanical	1 RCT	No	OR 7.09 (0.14 to 357.70)	NA
LMWH versus UFH	10 RCTs	Yes	OR 0.48 (0.24 to 0.95);	59.7
	1 RCT	No	1 trial evaluated this outcome at the post-discharge period and showed a RR 0.13 (0.01 to 1.17)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	7 RCTs	Yes	OR 0.28 (0.13 to 0.62)	0
▪ Limited to TKR	2 RCTs	No	1 trial had no events in the groups compared, the remaining trial showed OR 0.13 (0.01 to 2.13)	NA
▪ Limited to HFS	1 RCT	No	OR 7.95 (1.53 to 41.29)	NA
LMWH versus factor Xa inhibitor	1 RCT	No	OR 3.34 (0.58 to 19.32)	NA
LMWH versus DTI	3 RCTs	Yes	RR 1.18 (0.41 to 3.39)	0
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed an OR 3.89 (0.78 to 19.34)	NA
▪ Limited to 2001-present	2 RCTs	Yes	RR 1.25 (0.35 to 4.39)	0
▪ Limited to THR	2 RCTs	Yes	RR 1.03 (0.32 to 3.36)	0
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 2.00 (0.18 to 22.02)	NA
LMWH versus VKA	5 RCTs	Yes	OR 1.11 (0.57 to 2.19)	28.7
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed an OR 1.01 (0.06 to 16.14)	NA
▪ Limited to 2001-present	2 RCTs	Yes	OR 1.96 (0.20 to 18.94)	NA
▪ Limited to THR	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 1.23 (0.58 to 2.63)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to TKR	3 RCTs	Yes	OR 0.75 (0.17 to 3.31)	48.2
LMWH versus mechanical	1 RCT	No	OR 0.13 (0.003 to 6.72)	NA
UFH versus DTI	2 RCTs	Yes	OR 3.23 (0.56 to 18.98)	NA
▪ Limited to THR	2 RCTs	Yes	OR 3.23 (0.56 to 18.98)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Fatal pulmonary embolism				
Antiplatelet versus VKA	1 RCT, 1 OBS	No	RCT: OR 7.28 (0.14 to 366.83); observational data suggested a significantly higher percent of patients who received aspirin had a fatal pulmonary embolism than those who received warfarin	NA
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	10 RCTs	No	Nine trials had no events; the remaining trial showed OR 0.13 (0.003 to 6.73)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	7 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to TKR	1 RCT	No	OR 0.13 (0.003 to 6.73)	NA
▪ Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	OR 0.90 (0.38 to 2.13)	0
▪ Limited to 2001-present	4 RCTs	Yes	OR 0.90 (0.38 to 2.13)	0
▪ Limited to THR	2 RCTs	Yes	OR 1.00 (0.14 to 7.10)	NA
▪ Limited to TKR	1 RCT	No	OR 1.00 (0.06 to 16.01)	NA
▪ Limited to HFS	1 RCT	No	OR 0.86 (0.31 to 2.39)	NA
LMWH versus DTI	2 RCTs	Yes	OR 1.43 (0.08 to 24.82)	31.7
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed an OR 0.14 (0.003 to 6.97)	NA
▪ Limited to 2001-present	2 RCTs	Yes	OR 1.43 (0.08 to 24.82)	31.7
▪ Limited to THR	1 RCT (2 comparisons)	No	One arm of the trial had no events; the reaming arm showed OR 0.14 (0.003 to 6.91)	NA
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 4.00 (0.36 to 44.03)	NA
LMWH versus VKA	4 RCTs	No	Three trials had no events and 1 trial showed OR 7.29 (0.14 to 367.30)	NA
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period although no events occurred	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	One trials had no events; the remaining trial showed OR 7.29 (0.14 to 367.30)	NA
▪ Limited to TKR	2 RCTs	No	No events occurred in the groups compared	NA
LMWH versus mechanical	2 RCTs	Yes	One trial had no events; the remaining trial showed OR 0.14 (0.01 to 2.25)	NA
▪ Limited to 2001-present	1 RCT	No	OR 0.14 (0.01 to 2.25)	NA
▪ Limited to THR	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to TKR	1 RCT	No	OR 0.14 (0.01 to 2.25)	NA
UFH versus DTI	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Nonfatal pulmonary embolism				
Antiplatelet versus VKA	1 RCT, 1 OBS	No	RCT: No events occurred in the groups compared; observational data suggests no significant difference	NA
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	10 RCTs	Yes	OR 0.50 (0.25 to 1.00)	58.8
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed a RR 0.13 (0.01 to 1.17)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	7 RCTs	Yes	OR 0.28 (0.13 to 0.62)	0
▪ Limited to TKR	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.13 (0.003 to 6.73)	NA
▪ Limited to HFS	1 RCT	No	OR 7.95 (1.53 to 41.29)	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	OR 0.68 (0.34 to 1.37)	49.5
▪ Limited to 2001-present	4 RCTs	Yes	OR 0.68 (0.34 to 1.37)	49.5
▪ Limited to THR	2 RCTs	Yes	OR 0.39 (0.16 to 0.95)	NA
▪ Limited to TKR	1 RCT	No	OR 1.95 (0.39 to 9.72)	NA
▪ Limited to HFS	1 RCT	No	OR 1.32 (0.30 to 5.81)	NA
LMWH versus DTI	2 RCTs	Yes	OR 0.93 (0.23 to 3.66)	53.7
▪ Limited to 2001-present	2 RCTs	Yes	OR 0.93 (0.23 to 3.66)	53.7

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 1.61 (0.13 to 19.37)	NA
▪ Limited to TKR	1 RCT (2 comparisons)	No	One arm had no events; the remaining arm showed OR 0.14 (0.003 to 6.93)	NA
LMWH versus VKA	3 RCTs	Yes	OR 1.00 (0.20 to 4.95)	NA
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed an OR 1.01 (0.06 to 16.14)	NA
▪ Limited to 2001-present	1 RCT	No	OR 7.46 (0.46 to 120.00)	NA
▪ Limited to THR	1 RCT (2 comparisons)	No	No events occurred in the groups compared	NA
▪ Limited to TKR	2 RCTs	Yes	OR 1.00 (0.20 to 4.95)	NA
LMWH versus mechanical	1 RCT	No	OR 0.13 (0.003 to 6.72)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus DTI	2 RCTs	Yes	OR 3.27 (0.56 to 18.98)	NA
▪ Limited to THR	2 RCTs	Yes	OR 3.27 (0.56 to 18.98)	NA
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Post thrombotic Syndrome	0	---	---	---
Mortality				
Antiplatelet versus VKA	1 RCT, 2 OBS	No	RR 0.98 (0.32 to 3.05); observational data is conflicting with one study suggesting no significant difference and a second suggesting significantly higher percent of deaths in patients who received aspirin versus warfarin	NA
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	8 RCTs	Yes	OR 0.39 (0.10 to 1.49)	0
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	7 RCTs	Yes	OR 0.21 (0.03 to 1.59)	0
▪ Limited to HFS	1 RCT	No	RR 0.64 (0.13 to 3.06)	NA
LMWH versus factor Xa inhibitor	4 RCTs 1 OBS	Yes (RCTs)	RCT: OR 1.08 (0.72 to 1.60); observational data suggests significantly higher percent of deaths in patients who received LMWH versus factor Xa inhibitors	0
▪ Limited to 2001-present	4 RCTs	Yes	OR 1.08 (0.72 to 1.60)	0
▪ Limited to THR	2 RCTs	Yes	OR 0.88 (0.32 to 2.42)	NA
▪ Limited to TKR	1 RCT	No	OR 1.49 (0.26 to 8.65)	NA
▪ Limited to HFS	1 RCT	No	OR 1.10 (0.70 to 1.72)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus DTI	4 RCTs	Yes	RR 0.45 (0.15 to 1.36)	0
▪ Limited to 2001-present	3 RCTs	Yes	RR 0.54 (0.15 to 1.98)	0
▪ Limited to THR	2 RCTs	Yes	RR 0.27 (0.06 to 1.23)	0
▪ Limited to TKR	2 RCTs	Yes	RR 0.80 (0.16 to 4.17)	0
LMWH versus VKA	6 RCTs	Yes	OR 0.79 (0.42 to 1.50)	0
▪ Limited to 2001-present	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.37 (0.05 to 2.66)	NA
▪ Limited to THR	2 RCTs	Yes	RR 0.81 (0.36 to 1.82)	0
▪ Limited to TKR	3 RCTs	Yes	OR 0.52 (0.10 to 2.57)	NA
LMWH versus mechanical	2 RCTs	Yes	OR 0.31 (0.05 to 1.80)	NA
▪ Limited to 2001-present	1 RCT	No	OR 0.38 (0.05 to 2.73)	NA
▪ Limited to THR	1 RCT	No	OR 0.14 (0.003 to 7.01)	NA
▪ Limited to TKR	1 RCT	No	OR 0.38 (0.05 to 2.73)	NA
UFH versus DTI	2 RCTs	Yes	OR 7.13 (0.74 to 68.80)	NA
▪ Limited to THR	2 RCTs	Yes	OR 7.13 (0.74 to 68.80)	NA
UFH versus factor Xa inhibitor	1 OBS	No	Observational data suggested significantly higher percent of deaths in patients who received UFH versus factor Xa inhibitor	NA
UFH versus mechanical	1 RCT	No	OR 7.62 (0.15 to 384.19)	NA
VKA versus mechanical	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.95 (0.06 to 15.33)	NA
▪ Limited to THR	1 RCT	No	OR 0.95 (0.06 to 15.33)	
Mortality due to bleeding				
Antiplatelet versus VKA	1 RCT	No	No events occurred in the groups compared	NA
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	7 RCTs	No	Six trials had no events in the groups compared, the remaining trial showed OR 0.13 (0.003 to 6.52)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	6 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to HFS	1 RCT	No	OR 0.13 (0.003 to 6.52)	NA
LMWH versus factor Xa inhibitor	4 RCTs	No	Three trials had no events in the groups compared, the remaining trial showed OR 7.29 (0.14 to 367.58)	NA
▪ Limited to 2001-present	1 RCT	No	OR 7.29 (0.14 to 367.58)	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to HFS	1 RCT	No	OR 7.29 (0.14 to 367.58)	NA
LMWH versus DTI	3 RCTs	Yes	Two trials had no events in the groups compared, the remaining trial included two comparisons pooled to show RR 0.67 (0.07 to 6.40)	NA
▪ Limited to 2001-present	3 RCTs	Yes	Two trials had no events in the groups compared, the remaining trial included two comparisons pooled to show RR 0.67 (0.07 to 6.40)	NA
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 0.67 (0.07 to 6.40)	NA
▪ Limited to TKR	2 RCTs	No	No events occurred in the groups compared	NA
LMWH versus VKA	4 RCTs	No	Three trials had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 6.94)	NA
▪ Limited to 2001-present	1 RCT	No	OR 0.14 (0.003 to 6.94)	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to TKR	3 RCTs	No	Two trials had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 6.94)	NA
LMWH versus mechanical	2 RCTs	No	One trial had no events in the groups compared, the remaining trial showed OR 0.14 (0.003 to 7.01)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	1 RCT	No	OR 0.14 (0.003 to 7.01)	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
UFH versus DTI	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
VKA versus mechanical	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
Health related quality of life	0	---	---	---
Deep vein thrombosis				
Antiplatelet versus VKA	1 RCT	No	RR 1.06 (0.87 to 1.30)	NA
▪ Gender	1 RCT	No	No significant difference	NA
Antiplatelet versus mechanical	2 RCTs	Yes	RR 1.63 (1.11 to 2.39)	0
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 1.63 (1.08 to 2.44)	NA
▪ Limited to HFS	1 RCT	No	RR 1.68 (0.55 to 5.19)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus UFH	13 RCTs	Yes	RR 0.80 (0.65 to 0.99)	34.3
	1 RCT (2 comparisons)	Yes	1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17)	NA
▪ Limited to 2001-present	1 RCT	No	OR 0.13 (0.01 to 2.15)	NA
▪ Limited to THR	10 RCTs	Yes	RR 0.75 (0.58 to 0.97)	26.4
	1 RCT	No	1 trial ineligible for pooling showed RR 1.60 (0.21 to 12.06)	NA
▪ Limited to TKR	2 RCTs	Yes	RR 0.75 (0.58 to 0.96)	NA
	1 RCT	No	1 trial ineligible for pooling showed RR 6.00 (0.99 to 37.43)	NA
▪ Limited to HFS	1 RCT	No	RR 2.19 (1.01 to 4.98)	NA
▪ Age	1 RCT	No	Age did not impact the risk of DVT when comparing LMWH vs. UFH	NA
▪ Gender	2 RCTs	No	Gender did not impact risk of DVT when comparing LMWH vs. UFH	NA
▪ Ethnicity	1RCT	No	In white patients, enoxaparin was significantly better at reducing the risk of DVT although this effect was not seen in blacks. Oriental patients and a category called “other” did not have any events therefore the impact could not be evaluated.	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	RR 2.06 (1.66 to 2.55)	35.5
▪ Limited to 2001-present	4 RCTs	Yes	RR 2.06 (1.66 to 2.55)	35.5
▪ Limited to THR	2 RCTs	Yes	OR 1.87 (1.43 to 2.44)	NA
▪ Limited to TKR	1 RCT	No	RR 2.18 (1.59 to 3.01)	NA
▪ Limited to HFS	1 RCT	No	RR 2.39 (1.75 to 3.28)	NA
LMWH versus DTI	1 RCT	No	RR 1.39 (1.15 to 1.68)	NA
LMWH versus VKA	5 RCTs	Yes	RR 0.66 (0.55 to 0.79)	60.9
▪ Limited to 2001-present	1 RCT	No	RR 0.57 (0.42 to 0.76)	NA
▪ Limited to THR	3 RCTs	Yes	RR 0.61 (0.44 to 0.84)	67.6
▪ Limited to TKR	3 RCTs	Yes	RR 0.71 (0.57 to 0.87)	57.2
LMWH versus mechanical	3 RCTs	Yes	RR 0.90 (0.71 to 1.14)	0
▪ Limited to 2001-present	1 RCT	No	RR 0.94 (0.72 to 1.21)	NA
▪ Limited to THR	2 RCTs	Yes	RR 0.75 (0.43 to 1.30)	NA
▪ Limited to TKR	1 RCT	No	RR 0.94 (0.72 to 1.21)	NA
UFH versus DTI	2 RCTs	Yes	RR 2.31 (1.34 to 4.00)	NA
▪ Limited to THR	2 RCTs	Yes	RR 2.31 (1.34 to 4.00)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	1 RCT	No	RR 2.63 (1.36 to 5.25)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
VKA versus mechanical	3 RCTs	Yes	RR 1.45 (0.75 to 2.82)	58.5
▪ Limited to THR	3 RCTs	Yes	RR 1.45 (0.75 to 2.82)	58.5
Asymptomatic DVT				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	1 RCT	No	OR 1.45 (0.24 to 8.56)	NA
LMWH versus UFH	2 RCTs	Yes	RR 0.70 (0.43 to 1.16)	NA
▪ Limited to THR	2 RCTs	Yes	RR 0.70 (0.43 to 1.16)	NA
LMWH versus factor Xa inhibitor	0	---	---	---
LMWH versus DTI	2 RCTs	Yes	RR 0.97 (0.85 to 1.10)	0
▪ Limited to 2001-present	2 RCTs	Yes	RR 0.97 (0.85 to 1.10)	0
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 1.08 (0.69 to 1.69)	NA
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 0.95 (0.83 to 1.09)	NA
LMWH versus VKA	1 RCT	No	RR 0.50 (0.28 to 0.88)	NA
LMWH versus mechanical	1 RCT	No	OR 1.00 (0.06 to 16.45)	NA
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Symptomatic DVT				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	1 RCT	No	OR 1.91 (0.37 to 9.75)	NA
LMWH versus UFH	3 RCTs	Yes	OR 0.62 (0.22 to 1.75)	0
	2 RCT	Yes	2 trials evaluated this outcome during the post discharge period and showed OR 1.96 (0.20 to 19.02)	NA
▪ Limited to THR	3 RCTs	Yes	OR 0.62 (0.22 to 1.75)	0
LMWH versus factor Xa inhibitor	5 RCTs	Yes	OR 0.51 (0.22 to 1.21)	3.5
▪ Limited to 2001-present	5 RCTs	Yes	OR 0.51 (0.22 to 1.21)	3.5
▪ Limited to THR	2 RCTs	Yes	OR 0.21 (0.06 to 0.78)	NA
▪ Limited to TKR	2 RCTs	Yes	OR 1.01 (0.29 to 3.49)	NA
▪ Limited to HFS	1 RCT	No	OR 0.99 (0.06 to 15.83)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus DTI	3 RCTs	Yes	RR 0.98 (0.34 to 2.87)	47.5
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed OR 0.51 (0.14 to 1.91)	NA
▪ Limited to 2001-present	3 RCTs	Yes	RR 0.98 (0.34 to 2.87)	47.5
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 0.14 (0.02 to 1.03)	NA
▪ Limited to TKR	2 RCTs	Yes	RR 1.55 (0.58 to 4.20)	35
LMWH versus VKA	3 RCTs	Yes	OR 0.87 (0.61 to 1.24)	28.4
▪ Limited to 2001-present	1 RCT	No	OR 1.00 (0.06 to 16.09)	NA
▪ Limited to THR	2 RCTs	Yes	OR 0.87 (0.60 to 1.24)	52.5
▪ Limited to TKR	1 RCT	No	OR 1.00 (0.06 to16.09)	NA
LMWH versus mechanical	2 RCTs	No	One trial had no events; the remaining trials showed OR 7.28 (0.14 to 367.07)	NA
▪ Limited to THR	2 RCTs	No	One trial had no events; the remaining trials showed OR 7.28 (0.14 to 367.07)	NA
UFH versus DTI	1 RCT	No	This trial evaluated this outcome during the post-discharge period and showed OR 1.50 (0.26 to 8.74)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Proximal deep vein thrombosis				
Antiplatelet versus VKA	1 RCT	No	RR 0.78 (0.42 to 1.46)	NA
Antiplatelet versus mechanical	1 RCT	No	OR 0.57 (0.06 to 5.77)	NA
LMWH versus UFH	9 RCTs	Yes	RR 0.60 (0.38 to 0.93)	37
▪ Limited to THR	6 RCTs	Yes	RR 0.58 (0.39 to 0.86)	0
▪ Limited to TKR	2 RCTs	Yes	RR 0.32 (0.13 to 0.82)	NA
▪ Limited to HFS	1 RCT	No	RR 2.25 (0.95 to 5.61)	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	OR 2.24 (1.55 to 3.24)	73.5
▪ Limited to 2001-present	4 RCTs	Yes	OR 2.24 (1.55 to 3.24)	73.5
▪ Limited to THR	2 RCTs	Yes	OR 1.63 (0.95 to 2.80)	NA
▪ Limited to TKR	1 RCT	No	OR 2.18 (1.04 to 4.57)	NA
▪ Limited to HFS	1 RCT	No	OR 3.80 (1.92 to 7.50)	NA
LMWH versus DTI	2 RCTs	Yes	RR 0.91 (0.40 to 2.11)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to 2001-present	1 RCT (2 comparisons)	Yes	RR 0.58 (0.29 to 1.17)	NA
▪ Limited to THR	1 RCT	No	OR 1.71 (1.13 to 2.59)	NA
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 0.58 (0.29 to 1.17)	NA
LMWH versus VKA	6 RCTs	Yes	RR 0.63 (0.39 to 1.00)	55.3
▪ Limited to 2001-present	2 RCTs	Yes	RR 0.43 (0.05 to 4.11)	NA
▪ Limited to THR	3 RCTs	Yes	OR 0.67 (0.42 to 1.08)	NA
▪ Limited to TKR	4 RCTs	Yes	RR 0.63 (0.30 to 1.34)	68.9
LMWH versus mechanical	3 RCTs	Yes	RR 0.65 (0.34 to 1.26)	0
▪ Limited to 2001-present	1 RCT	No	OR 0.15 (0.02 to 1.05)	NA
▪ Limited to THR	2 RCTs	Yes	RR 0.71 (0.36 to 1.40)	NA
▪ Limited to TKR	1 RCT	No	OR 0.15 (0.02 to 1.05)	NA
UFH versus DTI	2 RCTs	Yes	OR 4.74 (2.99 to 7.49)	NA
▪ Limited to THR	2 RCTs	Yes	OR 4.74 (2.99 to 7.49)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	3 RCTs	Yes	RR 0.34 (0.16 to 0.73)	0
▪ Limited to THR	3 RCTs	Yes	RR 0.34 (0.16 to 0.73)	0
Distal deep vein thrombosis				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	1 RCT	No	RR 1.79 (1.15 to 2.79)	NA
LMWH versus UFH	8 RCTs	Yes	RR 0.95 (0.74 to 1.23)	0
▪ Limited to THR	5 RCTs	Yes	RR 1.03 (0.58 to 1.83)	0
▪ Limited to TKR	2 RCTs	Yes	RR 0.93 (0.69 to 1.24)	NA
▪ Limited to HFS	1 RCT	No	OR 1.86 (0.19 to 18.65)	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	RR 2.08 (1.72 to 2.52)	0
▪ Limited to 2001-present	4 RCTs	Yes	RR 2.08 (1.72 to 2.52)	0
▪ Limited to THR	2 RCTs	Yes	OR 1.90 (1.42 to 2.56)	NA
▪ Limited to TKR	1 RCT	No	RR 2.27 (1.57 to 3.28)	NA
▪ Limited to HFS	1 RCT	No	RR 2.24 (1.59 to 3.17)	NA
LMWH versus DTI	1 RCT	No	RR 0.79 (0.67 to 0.93)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus VKA	2 RCTs	Yes	RR 0.56 (0.43 to 0.73)	NA
▪ Limited to 2001-present	1 RCT	No	RR 0.60 (0.44 to 0.81)	NA
▪ Limited to THR	1 RCT	No	RR 0.48 (0.30 to 0.78)	NA
▪ Limited to TKR	1 RCT	No	RR 0.60 (0.44 to 0.81)	NA
LMWH versus mechanical	3 RCTs	Yes	RR 1.00 (0.77 to 1.29)	NA
▪ Limited to 2001-present	1 RCT	No	RR 1.01 (0.77 to 1.31)	NA
▪ Limited to THR	2 RCTs	No	One trial had no events in the groups compared, the other showed OR 0.84 (0.28 to 2.55)	NA
▪ Limited to TKR	1 RCT	No	RR 1.01 (0.77 to 1.31)	NA
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	OR 3.30 (0.91 to 11.91)	NA
Major Bleeding				
Antiplatelet versus VKA	1 RCT	No	RR 0.20 (0.03 to 1.23)	NA
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	7 RCTs	Yes	OR 0.57 (0.37 to 0.88)	37.1
▪ Limited to 2001-present	1 RCT	No	OR 7.54 (0.47 to 122.28)	NA
▪ Limited to THR	6 RCTs	Yes	OR 0.54 (0.34 to 0.85)	43.5
▪ Limited to TKR	1 RCT	No	OR 0.99 (0.20 to 4.93)	NA
LMWH versus factor Xa inhibitor	4 RCTs 1 OBS	Yes (RCT)	RCT: OR 0.65 (0.48 to 0.89); observational data suggested no significant difference	56.6
▪ Limited to 2001-present	4 RCTs	Yes	OR 0.65 (0.48 to 0.89)	56.6
▪ Limited to THR	2 RCTs	Yes	OR 0.64 (0.44 to 0.94)	NA
▪ Limited to TKR	1 RCT	No	OR 0.19 (0.06 to 0.58)	NA
▪ Limited to HFS	1 RCT	No	OR 1.04 (0.54 to 2.00)	NA
LMWH versus DTI	4 RCTs	Yes	RR 1.12 (0.80 to 1.57)	0
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed RR 0.51 (0.06 to 4.58)	NA
▪ Limited to 2001-present	3 RCTs	Yes	RR 1.17 (0.79 to 1.75)	0
▪ Limited to THR	2 RCTs	Yes	RR 0.97 (0.64 to 1.48)	0
▪ Limited to TKR	2 RCTs	Yes	RR 1.46 (0.82 to 2.59)	0

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus VKA	7 RCTs	Yes	OR 1.92 (1.27 to 2.91)	0
	1 RCT (2 comparisons)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8	NA
▪ Limited to 2001-present	2 RCTs	Yes	One trial had no events; the remaining trial showed OR 2.26 (0.75 to 6.83)	NA
▪ Limited to THR	3 RCTs	Yes	OR 1.91 (1.11 to 3.29)	0
	1 RCT (2 comparisons)	Yes	1 trial ineligible for pooling showed a RR 1.51 (0.92 to 2.48) for major bleeding days 0-1 and a RR 3.41 (0.77 to 15.18) for major bleeding on days 2-8	NA
▪ Limited to TKR	4 RCTs	Yes	OR 1.93 (1.01 to 3.67)	0
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	1 OBS	No	Observational data suggests major bleeding was significantly increased in patients who received UFH versus injectable or oral factor Xa inhibitor	NA
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Major bleeding leading to reoperation				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	1 RCT	No	No events occurred in the groups compared	NA
LMWH versus factor Xa inhibitor	4 RCTs	Yes	OR 0.67 (0.28 to 1.61)	0
▪ Limited to 2001-present	4 RCTs	Yes	OR 0.67 (0.28 to 1.61)	0
▪ Limited to THR	2 RCTs	Yes	OR 0.72 (0.23 to 2.23)	0
▪ Limited to TKR	1 RCT	No	OR 0.51 (0.05 to 4.94)	NA
▪ Limited to HFS	1 RCT	No	OR 0.66 (0.11 to 3.82)	NA
LMWH versus DTI	3 RCTs	Yes	RR 1.27 (0.43 to 3.75)	0
▪ Limited to 2001-present	3 RCTs	Yes	RR 1.27 (0.43 to 3.75)	0
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 1.21 (0.29 to 5.08)	NA
▪ Limited to TKR	2 RCTs	Yes	RR 1.36 (0.27 to 7.03)	0
LMWH versus VKA	2 RCTs	No	One trial had no events; the remaining trial showed OR 7.61 (0.15 to 383.70)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
▪ Limited to THR	1 RCT	No	OR 7.61 (0.15 to 383.70)	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.51 (0.10 to 2.55)	NA
▪ Limited to THR	2 RCTs	No	One trial had no events; the remaining trial showed OR 0.51 (0.10 to 2.55)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Minor Bleeding				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	5 RCTs	Yes	RR 0.90 (0.63 to 1.28)	9.9
▪ Limited to 2001-present	1 RCT	No	RR 0.25 (0.03 to 2.16)	NA
▪ Limited to THR	4 RCTs	Yes	OR 0.92 (0.57 to 1.51)	31.4
▪ Limited to TKR	1 RCT	No	RR 0.87 (0.60 to 1.25)	NA
LMWH versus factor Xa inhibitor	1 RCT	No	OR 0.52 (0.30 to 0.91)	NA
LMWH versus DTI	3 RCTs	Yes	RR: 1.07 (0.89 to 1.29)	0
	1 RCT	No	1 trial evaluated this outcome during the post-discharge period and showed a RR 0.54 (0.15 to 1.94)	NA
▪ Limited to 2001-present	3 RCTs	Yes	RR 1.07 (0.89 to 1.29)	0
▪ Limited to THR	1 RCT (2 Comparisons)	Yes	RR 1.04 (0.79 to 1.37)	NA
▪ Limited to TKR	2 RCTs	Yes	RR 1.10 (0.86 to 1.40)	0
LMWH versus VKA	7 RCTs	Yes	RR 1.23 (1.06 to 1.43)	0
	1 RCT (2 comparisons)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8	NA
▪ Limited to 2001-present	2 RCTs	Yes	RR 1.25 (0.85 to 1.83)	NA
▪ Limited to THR	3 RCTs	Yes	RR 1.26 (0.85 to 1.86)	27.8
	1 RCT (2 comparisons)	Yes	1 trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37)] on days 0-1 and a RR 0.87 (0.37 to 2.06) on days 2-8	NA
▪ Limited to TKR	4 RCTs	Yes	RR 1.17 (0.95 to 1.43)	0
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	2 RCTs	Yes	OR 0.80 (0.26 to 2.41)	NA
▪ Limited to THR	2 RCTs	Yes	OR 0.80 (0.26 to 2.41)	NA
Surgical site bleeding				
Antiplatelet versus VKA	1 OBS	No	Observational data suggests no significant difference	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	3 RCTs	Yes	OR 0.92 (0.46 to 1.82)	41.1
▪ Limited to 2001-present	1 RCT	No	RR 0.75 (0.20 to 2.86)	NA
▪ Limited to THR	2 RCTs	Yes	RR 0.63 (0.26 to 1.55)	3.1
▪ Limited to TKR	1 RCT	No	OR 1.78 (0.61 to 5.14)	NA
LMWH versus factor Xa inhibitor	1 RCT	No	OR 0.72 (0.45 to 1.17)	NA
LMWH versus DTI	1 RCT	No	RR 4.35 (1.51 to 12.54)	NA
LMWH versus VKA	2 RCT	Yes	OR 2.63 (1.31 to 5.28)	NA
▪ Limited to 2001-present	1 RCT	No	OR 2.05 (0.80 to 5.29)	NA
▪ Limited to THR	1 RCT	No	OR 3.35 (1.27 to 9.84)	NA
▪ Limited to TKR	1 RCT	No	OR 2.05 (0.80 to 5.29)	NA
▪ Major surgical site bleeding	2 RCTs	Yes	OR 2.51 (1.38 to 4.54)	NA
	1 RCT (2 comparisons)	Yes	1 trial ineligible for original pooled analysis showed a RR 1.72 (1.02 to 2.92) on days 0-1 and a RR 2.72 (0.59 to 12.44) on days 2-8	NA
▪ Minor surgical site bleeding	2 RCTs	Yes	OR 1.34 (0.91 to 1.97)	NA
	1 RCT (2 comparisons)	Yes	1 trial ineligible for pooling showed an OR 7.42 (0.15 to 373.92) on days 0-1 and an OR 7.43 (0.46 to 119.03) on days 2-8	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	1 RCT	No	OR 0.87 (0.31 to 2.43)	NA
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Bleeding leading to infection	0	---	---	---
Bleeding leading to transfusion				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus UFH	0	---	---	---
LMWH versus factor Xa inhibitor	0	---	---	---
LMWH versus DTI	2 RCTs	Yes	RR 1.00 (0.59 to 1.69)	0
▪ Limited to 2001-present	2 RCTs	Yes	RR 1.00 (0.59 to 1.69)	0
▪ Limited to THR	1 RCT (2 comparisons)	Yes	RR 1.19 (0.46 to 3.10)	NA
▪ Limited to TKR	1 RCT (2 comparisons)	Yes	RR 0.71 (0.26 to 1.98)	NA
LMWH versus VKA	1 RCT	No	OR 1.71 (0.42 to 6.90)	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	No events occurred in the groups compared	NA
Heparin induced thrombocytopenia				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	3 RCTs	Yes	OR 0.13 (0.03 to 0.43)	0
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	3 RCTs	Yes	OR 0.13 (0.03 to 0.43)	0
LMWH versus factor Xa inhibitor	0	---	---	---
LMWH versus DTI	0	---	---	---
LMWH versus VKA	1 RCT	No	No events occurred in the groups compared	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---
Discomfort				
Antiplatelet versus VKA	0	---	---	--
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	0	---	---	--

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus factor Xa inhibitor	0	---	---	--
LMWH versus DTI	0	---	---	--
LMWH versus VKA	0	---	---	--
LMWH versus mechanical	1 RCT	No	RR 0.49 (0.29 to 0.82)	NA
UFH versus DTI	0	---	---	--
UFH versus factor Xa inhibitor	0	---	---	--
UFH versus mechanical	0	---	---	--
VKA versus mechanical	0	---	---	--
Readmission				
Antiplatelet versus VKA	0	---	---	--
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	2 RCT	Yes	RR 0.82 (0.20 to 3.38)	14.2
▪ Limited to 2001-present	1 RCT	No	OR 7.54 (0.47 to 122.23)	NA
▪ Limited to THR	2 RCT	Yes	RR 0.82 (0.20 to 3.38)	14.2
LMWH versus factor Xa inhibitor	0	---	---	---
LMWH versus DTI	0	---	---	---
LMWH versus VKA	0	---	---	---
LMWH versus mechanical	2 RCT	Yes	OR 0.83 (0.22 to 3.11)	NA
▪ Limited to 2001-present	1 RCT	No	OR 0.78 (0.17 to 3.50)	NA
▪ Limited to THR	1 RCT	No	OR 0.78 (0.17 to 3.50)	NA
▪ Limited to TKR	1 RCT	No	OR 1.03 (0.06 to 16.52)	NA
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	1 RCT	No	OR 0.15 (0.003 to 7.58)	NA
Reoperation				
Antiplatelet versus VKA	0	---	---	---
Antiplatelet versus mechanical	0	---	---	---
LMWH versus UFH	0	---	---	---
LMWH versus factor Xa inhibitor	1 RCT	No	RR 0.25 (0.04 to 1.63)	NA
LMWH versus DTI	0	---	---	---

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity: I^2 (%)
LMWH versus VKA	2 RCT	No	One trial had no events in the groups compared, the remaining trial showed RR 0.85 (0.59 to 1.22)	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	1 RCT	No	RR 0.85 (0.59 to 1.22)	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
LMWH versus mechanical	0	---	---	---
UFH versus DTI	0	---	---	---
UFH versus factor Xa inhibitor	0	---	---	---
UFH versus mechanical	0	---	---	---
VKA versus mechanical	0	---	---	---

*: All base case analyses are represented in the table. When only 1 trial or study was available subgroup analyses were not run. Subgroup analyses with no available data are not represented in this table.

Abbreviations: DTI=direct thrombin inhibitor; HFS=hip fracture surgery; LMWH=low molecular weight heparin; NA=Not Applicable; OBS=observational; OR=Peto's Odds Ratio; RCT=Randomized Controlled Trial; RR=Relative Risk; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VKA=vitamin K antagonist

Key Question 6

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

Key Points

- The literature base for intraclass comparisons of therapy is not as extensive as the interclass comparisons in Key Question 5.
- Venous thromboembolism (symptomatic, major), postthrombotic syndrome, health related quality of life, major bleeding leading to reoperation, bleeding leading to infection, bleeding leading to transfusion, discomfort, reoperation, or readmission outcomes could not be evaluated due to lack of trials or studies evaluating these endpoints.
- For pulmonary embolism, the single trial comparing low molecular weight heparins and two of the three trials comparing mechanical prophylaxis had no events in either group. In the one trial with events, no significant differences were found between the Venaflow and Kendall devices, although the confidence intervals were very large.
- For fatal pulmonary embolism, one of two trials comparing low molecular weight heparins and all three trials comparing mechanical prophylaxis had no events in either group. In the one trial with events, no significant differences were found between enoxaparin and tinzaparin although the confidence intervals were very large.
    - One observational trial comparing mechanical prophylactic devices also did not have any fatal pulmonary embolism events.
- For nonfatal pulmonary embolism, one of two trials comparing low molecular weight heparins and two of three trials comparing mechanical prophylaxis had no events in either group. In the one low molecular weight heparin trial with events, no significant differences were found between enoxaparin and tinzaparin although the confidence intervals were very large. In the one mechanical prophylaxis trial, no significant differences were found between the Venaflow and Kendall devices, although the confidence intervals were very large.
    - One observational study comparing the ActiveCare system versus the Flowtron pump mechanical devices found no significant differences between groups in the occurrence of nonfatal pulmonary embolism. Very low rates occurred in both groups (0 percent versus 0.7 percent, p=0.459).

- One trial found no difference in mortality between enoxaparin and tinzaparin while another trial found no difference between the Venaflow and Kendall devices. The confidence intervals for these evaluations were very large.
    - No events occurred in an observational study comparing mechanical prophylaxis devices.
- For mortality due to bleeding, one trial comparing low molecular weight heparins and one trial and one observational study evaluated the impact of mechanical prophylaxis strategies. No events occurred in either group in these evaluations.
- More data is available regarding the comparison of drugs within a class on the occurrence of deep venous thrombosis, proximal deep venous thrombosis, and distal deep venous thrombosis.
    - No difference in the occurrence of deep venous thrombosis occurred in the pooled analysis comparing enoxaparin versus either tinzaparin or dalteparin.
    - The Venaflow pneumatic compression device significantly reduced the occurrence of deep venous thrombosis versus the Kendall pneumatic compression device in the only trial.
        - The same results were found when trials were limited to the years 2001 to the present and to total knee replacement surgery.
    - Intermittent compression stockings significantly reduce the occurrence of deep venous thrombosis versus graduated compression stockings in the only trial.
        - The same results were found when trials were limited to the years 2001 to the present and to total hip replacement and total knee replacement surgery.
    - In the only observational study, two intermittent compression devices were compared (ActiveCare system versus Flowtron excel pump) and found to have a similar occurrence of deep venous thrombosis.
- For asymptomatic deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and dalteparin but no trials or observational studies compared mechanical devices.
- For symptomatic deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and tinzaparin but neither of the two trials comparing mechanical devices had events in either group.
- For proximal deep venous thrombosis, two trials compared low molecular weight heparins and found no significant difference between enoxaparin and either dalteparin or tinzaparin. In one trial comparing two different intermittent compression devices (Venoflow versus Kendall), no significant difference in the occurrence of proximal deep venous thrombosis occurred. Neither of the two trials comparing intermittent compressions stockings versus graduated compression stocking found a significant difference in the occurrence of proximal deep venous thrombosis.
- For distal deep venous thrombosis, one trial compared low molecular weight heparins and found no significant differences between enoxaparin and tinzaparin. In one trial, the occurrence of distal deep venous thrombosis was significantly lower with the Venaflow intermittent compression device than with the Kendall intermittent compression device. In a trial, the occurrence of distal deep venous thrombosis was lower with intermittent compression stockings versus graduated compression stockings. Both of the mechanical

intervention trials were conducted from 2001 to the present and included patients with total hip and total knee replacement surgery.

- For major bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. No trials or studies evaluated the impact of mechanical interventions on this endpoint.
- For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. No trials or studies evaluated mechanical interventions on this endpoint.
- For surgical site bleeding, two trials compared low molecular weight heparins and found no differences between enoxaparin and either dalteparin or tinzaparin. No trials or studies evaluated the impact of mechanical interventions on this endpoint.
- For heparin induced thrombocytopenia, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. No trials or studies evaluated mechanical interventions on this endpoint.

Detailed Analysis

Study design and characteristics. Five randomized controlled trials (N=1285) and one controlled observational study (N=1577) evaluated the comparative efficacy within the classes of injectable low molecular weight heparin agents and mechanical devices.[20,101,103,106,133,141] All five trials were published as full text manuscripts. Two trials compared injectable low molecular weight heparin agents (N= 631),[20,101] two trials compared mechanical prophylaxes (N=523)[103,133] and one trial compared mechanical prophylaxes with all patients receiving enoxaparin prophylaxis also (N=131).[106] The observational study compared mechanical prophylaxes (N=1577).[141] Two trials enrolled patients who had total hip replacement surgery (N= 599),[20,105] one trial enrolled patients who had total knee replacement surgery (N= 423),[103] one trial enrolled patients who had hip fracture surgery (N=132),[101] and one trial enrolled patients who had either total hip replacement or total knee replacement surgery (N=131).[106] The observational study also enrolled patients who had total hip replacement or total knee replacement surgery (N=1577).[141] The earliest study was published in 1998[133] and the most recent study was published in 2009.[141] The duration of followup ranged from postoperative period to 180 days. Four trials received funding from the industry,[20,103,106,133] one trial received funding from government and foundation[101] and the observational study was unfunded.[141]

The mean age of enrolled patients ranged from 63.0 years to 77 years. Females represented between 55.24 and 78.79 percent of the enrolled populations. The mean weight ranged from 71.0 to 87.7 kilograms. Few patients enrolled had a history of venous thromboembolism ranging from 3.1 to 9.0 percent. One study reported presence of varicosity ranging from 61.9 to 66.18 percent. The percent of patients with a history of malignancy ranged from 3.1 to 6.1 percent.

Seventy-seven to 100 percent of patients underwent primary surgery and one trial reported the percent of patients who had cemented fixation during surgery ranging from 42.65 to 46.03 percent. Mean duration of surgery ranged from 69.0 to 93.0 minutes and the mean duration of anesthesia ranged from 133 to 161 minutes. Use of general anesthesia ranged from 11.98 to 27.94 percent and use of regional anesthesia ranged from 72.0 to 100.0 percent of patients. The mean length of hospital stay was reported by the observational study ranging from 4.2 to 5 days.

Outcome evaluations. A summary of the results is presented in Table 13.

Symptomatic objectively confirmed venous thromboembolism

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Major venous thromboembolism

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Pulmonary embolism

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between enoxaparin and dalteparin on pulmonary embolism in patients who had hip fracture surgery although no events occurred therefore the risk of pulmonary embolism could not be calculated.[101]

Mechanical prophylaxis. Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on pulmonary embolism in patients who had major orthopedic surgery.[103,106,133] Two trials that evaluated intermittent pneumatic compression versus graduated compression stockings did not have events occur in the groups compared therefore the risk of pulmonary embolism could not be evaluated.[106,133] One trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery.[103] In this trial, the odds of pulmonary embolism were not significantly different [OR 0.14 (0.003 to 7.18)] in patients who received the Venaflow device versus the Kendall device.

Fatal pulmonary embolism

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on fatal pulmonary embolism in patients who had major orthopedic surgery.[20,101] One trial was excluded from the analysis because no events occurred.[101] The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip

replacement surgery.[20] In this trial, the odds of fatal pulmonary embolism were not significantly different [OR 7.48 (0.15 to 376.94)] in patients who received enoxaparin versus tinzaparin.

Mechanical prophylaxis. Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on pulmonary embolism in patients who had major orthopedic surgery although no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.[103,106,133]

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on fatal pulmonary embolism in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of fatal pulmonary embolism could not be calculated.[141]

Nonfatal pulmonary embolism

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[20,101] One trial was excluded from the analysis because no events occurred.[101] The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip replacement surgery.[20] In this trial, the odds of nonfatal pulmonary embolism were not significantly different [OR 1.01 (0.06 to 16.23] in patients who received enoxaparin versus tinzaparin.

Mechanical prophylaxis. Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[103,106,133] Two trials that evaluated intermittent pneumatic compression versus graduated compression stockings did not have events occur in the groups compared therefore the risk of pulmonary embolism could not be evaluated.[106,133] One trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery.[103] In this trial, in patients who received the Venaflow device versus the Kendall device, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 7.18)].

One controlled observational study evaluated comparative efficacy between individual mechanical prophylaxis devices on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[141] Two intermittent pneumatic compression devices were compared in patients who had either total hip or knee replacement surgery; ActiveCare continuous enhanced circulatory system versus Flowtron excel pump. Patients also received enoxaparin (30mg twice daily for knee and 40mg daily for hip surgery) starting 12-24 hours postoperatively at the discretion of the clinical team however the percent of patients that did receive enoxaparin in each group was not reported. There was no significant difference in the percent of patients that developed a nonfatal pulmonary embolism in the ActiveCare group versus the Flowtron group (0 percent versus 0.7 percent, $p = 0.459$).

Postthrombotic syndrome

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Mortality

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on mortality in patients who had major orthopedic surgery.[20] This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of mortality were not significantly different [OR 7.48 (0.15 to 376.94)].

Mechanical prophylaxis. One randomized controlled trial evaluated the comparative efficacy between individual mechanical prophylaxis devices in patients who had major orthopedic surgery on this outcome.[103] This trial by Lachiewicz and colleagues in 2004 compared the Venaflow intermittent pneumatic compression device to the intermittent pneumatic compression device by Kendall in patients who had total knee replacement surgery. In patients who received the Venaflow device versus the Kendall device, the odds of mortality were not significantly different [OR 0.14 (0.003 to 7.18)].

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on mortality in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality could not be calculated.[141]

Mortality due to bleeding

Low molecular weight heparin agents. One randomized controlled evaluated the comparative efficacy between individual low molecular weight heparin agents on mortality due to bleeding in patients who had major orthopedic surgery although no events occurred therefore the risk of mortality due to bleeding could not be calculated.[20]

Mechanical prophylaxis. One randomized controlled trial evaluated the comparative efficacy between individual mechanical prophylaxis devices on mortality due to bleeding in patients who had major orthopedic surgery although no events occurred therefore the risk of mortality due to bleeding could not be calculated.[103]

One controlled observational study evaluated comparative efficacy between individual mechanical prophylaxis devices on mortality due to bleeding in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality due to bleeding could not be calculated.[141]

Health related quality of life

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Deep vein thrombosis

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on deep vein thrombosis in patients who had major orthopedic surgery.[20,101] The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the risk of deep vein thrombosis was not significantly different [RR 0.93 (0.64 to 1.33)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the risk of deep vein thrombosis was not significantly different [RR 1.75 (0.64 to 4.84)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the risk of deep vein thrombosis was not significantly different [RR 1.05 (0.64 to 1.71)] (Appendix Figure 206). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

Mechanical prophylaxis. Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on deep vein thrombosis in patients who had major orthopedic surgery.[103,106] The first trial by Lachiewicz and colleagues in 2004 compared to intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on in which patients received the Venaflow device versus the Kendall device for prophylaxis, the risk of deep vein thrombosis was significantly decreased [RR 0.46 (0.26 to 0.79), NNT 13].

The second trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.[106] In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of deep vein thrombosis was significantly decreased [RR 0.09 (0.01 to 0.92), NNT 7]. In the patients who had total knee replacement surgery and received

intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of deep vein thrombosis was significantly decreased [RR 0.03 (0.004 to 0.31), NNT 3]. When pooling these two surgical populations to compare intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, in patients who had major orthopedic surgery, the risk of deep vein thrombosis was significantly decreased [RR 0.06 (0.01 to 0.42), NNT 3 to 7] (Appendix Figure 207). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

One controlled observational study evaluated the comparative efficacy between individual mechanical prophylaxis devices on deep vein thrombosis in patients who had major orthopedic surgery.[141] Two intermittent pneumatic compression devices were compared in patients who had either total hip or knee replacement surgery; ActiveCare continuous enhanced circulatory system versus Flowtron excel pump. Patients also received enoxaparin (30mg twice daily for knee and 40mg daily for hip surgery) starting 12-24 hours postoperatively at the discretion of the clinical team however the percent of patients that did receive enoxaparin in each group was not reported. In patients who received the ActiveCare device versus the Flowtron device, there was no significant difference in the risk of deep vein thrombosis (1.35 percent versus 3.62 percent, p = 0.119).

Asymptomatic deep vein thrombosis

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[101] This trial by the TIFDED study group in 1999 compared enoxaparin to dalteparin in patients who had hip fracture surgery. In this trial, the risk of asymptomatic deep vein thrombosis was not significantly different [RR 1.75 (0.64 to 4.84)] in patients who received enoxaparin versus dalteparin.

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

Symptomatic deep vein thrombosis

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[20,101] One trial was excluded from the analysis because no events occurred.[101] The remaining trial by Planes and colleagues in 1999 evaluated the comparative efficacy of enoxaparin to tinzaparin in patients who had total hip replacement surgery.[20] In this trial, the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.51 (0.26 to 8.79)] in patients who received enoxaparin versus tinzaparin.

Mechanical prophylaxis. Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on symptomatic deep vein

thrombosis in patients who had major orthopedic surgery.[103,133] One trial evaluated this outcome during the post discharge period.[103] However, in both trials, no events occurred in the groups compared therefore the risk of symptomatic deep vein thrombosis could not be calculated.[103,133]

Proximal deep vein thrombosis

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on proximal deep vein thrombosis in patients who had major orthopedic surgery.[20,101] The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, the odds of proximal deep vein thrombosis were not significantly different [OR 1.12 (0.60 to 2.08)] in patients who received enoxaparin versus dalteparin. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, the odds of proximal deep vein thrombosis were not significantly different [OR 0.73 (0.12 to 4.34)] in patients who received enoxaparin versus tinzaparin. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the risk of proximal deep vein thrombosis was not significantly different [RR 1.06 (0.62 to 1.81)] (Appendix Figure 208). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

Mechanical prophylaxis. Three randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on proximal deep vein thrombosis in patients who had major orthopedic surgery.[103,106,133] The first trial by Lachiewicz and colleagues in 2004 compared to intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on, in which patients received the Venaflow device versus the Kendall device for prophylaxis, the odds of proximal deep vein thrombosis were not significantly different [OR 0.24 (0.05 to 1.08)].

The second trial by Ryan and colleagues in 1998 compared intermittent pneumatic compression versus graduated compression stockings in patients who had total hip replacement surgery. [133] In this trial, in patients who received intermittent pneumatic compression versus graduated compression stockings the risk of proximal deep vein thrombosis was not significantly different [RR 0.36 (0.13 to 1.00)].

The third trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.[106] In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the odds of proximal deep vein thrombosis were not significantly different [OR 0.11 (0.002 to 5.78)]. In the patients who had total knee replacement surgery and

received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the odds of proximal deep vein thrombosis were not significantly different [OR 0.14 (0.003 to 6.82)]. When pooling these two surgical populations to evaluate the comparison of intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, in patients who had major orthopedic surgery, the odds of proximal deep vein thrombosis were not significantly different [OR 0.12 (0.01 to 1.99)] (Appendix Figure 209). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

Distal deep vein thrombosis

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on distal deep vein thrombosis in patients who had major orthopedic surgery.[20] This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the risk of distal deep vein thrombosis was not significantly different [RR 0.78 (0.46 to 1.34)].

Mechanical prophylaxis. Two randomized controlled trials evaluated the comparative efficacy between individual mechanical prophylaxis devices on distal deep vein thrombosis in patients who had major orthopedic surgery.[103,106] The first trial by Lachiewicz and colleagues in 2004 compared to intermittent pneumatic compression devices to each other; the Venaflow intermittent pneumatic compression device and the intermittent pneumatic compression device by Kendall, in patients who had total knee replacement surgery. Outcomes were reported in terms of number of knees with deep vein thrombosis out of the total number of knees operated on. In the knees operated on in which patients received the Venaflow device versus the Kendall device for prophylaxis, the risk of distal deep vein thrombosis was significantly decreased [RR 0.52 (0.29 to 0.93), NNT 35].

The second trial by Silbersack and colleagues in 2004 compared enoxaparin plus intermittent pneumatic compression to enoxaparin plus graduated compression stockings in patients who had total hip or total knee replacement surgery, and outcomes were reported separately for each surgical population.[106] In the patients who had total hip replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of distal deep vein thrombosis was not significantly different [RR 0.15 (0.01 to 1.53)]. In the patients who had total knee replacement surgery and received intermittent pneumatic compression versus graduated compression stockings; both in combination with enoxaparin, the risk of distal deep vein thrombosis was significantly decreased [RR 0.04 (0.004 to 0.33), NNT 3]. When pooling these two surgical populations to compare intermittent pneumatic compression versus graduated compression stockings, both in combination with enoxaparin in patients who had major orthopedic surgery, the risk of distal deep vein thrombosis was significantly decreased [RR 0.07 (0.01 to 0.54), NNT 3 to 11] (Appendix Figure 210). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

Major bleeding

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on major bleeding in patients who had major orthopedic surgery.[20,101] The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the odds of major bleeding were not significantly different [OR 1.98 (0.40 to 9.91)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of major bleeding were not significantly different [OR 1.97 (0.20 to 19.25)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the odds of major bleeding were not significantly different [RR 1.98 (0.53 to 7.37)] (Appendix Figure 211). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did no report data based on these subgroups.

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

Major bleeding leading to reoperation

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Minor bleeding

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on minor bleeding in patients who had major orthopedic surgery.[20] This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of minor bleeding were not significantly different [OR 1.67 (0.84 to 3.36)].

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

Surgical site bleeding

Low molecular weight heparin agents. Two randomized controlled trials evaluated the comparative efficacy between individual low molecular weight heparin agents on surgical site bleeding in patients who had major orthopedic surgery.[20,101] The first trial by Planes and colleagues in 1999 compared enoxaparin versus dalteparin in patients who had hip fracture surgery. In this trial, in patients who received enoxaparin versus dalteparin, the odds of surgical site bleeding were not significantly different [OR 1.98 (0.40 to 9.91)]. The second trial by the TIFDED study group compared enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of surgical site bleeding were not significantly different [OR 0.14 (0.003 to 6.82)]. When pooling these two trials to evaluate the comparative efficacy on enoxaparin versus other low molecular weight heparin agents in patients who had major orthopedic surgery, the odds of surgical site bleeding were not significantly different [RR 1.35 (0.30 to 5.97)] (Appendix Figure 212). Statistical heterogeneity and publication bias could not be evaluated because of too few studies. Subgroup analysis based on trial published from 2001-present was not possible since both trial were published prior to 2001. Subgroup analyses based on age, gender or ethnicity were not possible because the trials did not report data based on these subgroups.

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

Bleeding leading to infection

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Bleeding leading to transfusion

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Heparin induced thrombocytopenia

Low molecular weight heparin agents. One randomized controlled trial evaluated the comparative efficacy between individual low molecular weight heparin agents on heparin induced thrombocytopenia in patients who had major orthopedic surgery.[20] This trial by Planes and colleagues evaluated enoxaparin versus tinzaparin in patients who had total hip replacement surgery. In this trial, in patients who received enoxaparin versus tinzaparin the odds of heparin induced thrombocytopenia were not significantly different [OR 7.48 (0.15 to 376.94)].

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

Discomfort

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Readmission

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Reoperation

Low molecular weight heparin agents. No randomized controlled trials or controlled observational studies evaluated the comparative efficacy between individual low molecular weight heparin agents in patients who had major orthopedic surgery on this outcome.

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

Table 13. Summary of results of key question 6*

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Symptomatic objectively confirmed VTE				
Enoxaparin versus LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Major VTE				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
PE				
Enoxaparin versus other LMWH	1 RCT	No	No events occurred in the groups compared	NA
IPC versus IPC	1 RCT	No	OR 0.14 (0.003 to 7.18)	NA
IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
Fatal PE				
Enoxaparin versus other LMWH	2 RCTs	No	One trial had no events; remaining one trial showed OR 7.48 (0.15 to 376.94)	NA
▪ Limited to THR	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
▪ Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
IPC versus IPC	1 RCT, 1 OBS	No	No events occurred in the groups compared	NA
IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
Nonfatal PE				
Enoxaparin versus other LMWH	2 RCTs	No	One trial had no events; remaining one trial showed OR 1.01 (0.06 to 16.23)	NA
▪ Limited to THR	1 RCT	No	OR 1.01 (0.06 to 16.23)	NA
▪ Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
IPC versus IPC	1 RCT, 1 OBS	No	OR 0.14 (0.003 to 7.18); observational data suggests no significant difference in the percent of patients that developed a nonfatal PE in the ActiveCare group versus the Flowtron group	NA
IPC versus GCS	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to 2001-present	1 RCT	No	No events occurred in the groups compared	NA
▪ Limited to THR	2 RCTs	No	No events occurred in the groups compared	NA
▪ Limited to TKR	1 RCT	No	No events occurred in the groups compared	NA
PTS	0	---	---	---
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Mortality				
Enoxaparin versus other LMWH	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
IPC versus IPC	1 RCT, 1 OBS	No	OR 0.14 (0.003 to 7.18); In the observational study, no events occurred in the groups compared	NA
IPC versus GCS	0	---	---	---
Mortality due to bleeding				
Enoxaparin versus other LMWH	1 RCT	No	No events occurred in the groups compared	NA
IPC versus IPC	1 RCT, 1 OBS	No	No events occurred in the groups compared	NA
IPC versus GCS	0	---	---	---
HRQOL				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
DVT				
Enoxaparin versus other LMWH	2 RCTs	Yes	RR 1.05 (0.64 to 1.71)	NA
▪ Limited to THR	1 RCT	No	RR 1.75 (0.64 to 4.84)	NA
▪ Limited to HFS	1 RCT	No	RR 0.93 (0.64 to 1.33)	NA
IPC versus IPC	1 RCT, 1 OBS	No	1 trial evaluated this outcome in total knees operated and showed RR 0.46 (0.26 to 0.79); observational data suggests no significant difference in the risk of DVT in patients who received ActiveCare device versus Flowtron	NA
IPC versus GCS	1 RCT (2 comp)	Yes	RR 0.06 (0.01 to 0.42)	NA
▪ Limited to 2001-present	1 RCT (2 comp)	Yes	RR 0.06 (0.01 to 0.42)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ Limited to THR	1 RCT (1 comp)	No	RR 0.09 (0.01 to 0.92)	NA
▪ Limited to TKR	1 RCT (1 comp)	No	RR 0.03 (0.004 to 0.31)	NA
▪ Limited to HFS	0	---	---	---
Asymptomatic DVT				
Enoxaparin versus other LMWH	1 RCT	No	RR 1.75 (0.64 to 4.84)	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Symptomatic DVT				
Enoxaparin versus other LMWH	2 RCTs	No	1 trial had no events; remaining trial showed OR 1.51 (0.26 to 8.79)	NA
▪ Limited to THR	1 RCT	No	OR 1.51 (0.26 to 8.79)	NA
▪ Limited to HFS	1 RCT	No	No events occurred in the groups compared	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	1 RCT	No	No events occurred in the groups compared	NA
Proximal DVT				
Enoxaparin versus other LMWH	2 RCTs	Yes	RR 1.06 (0.62 to 1.81)	NA
▪ Limited to THR	1 RCT	No	OR 0.73 (0.12 to 4.34)	NA
▪ Limited to HFS	1 RCT	No	OR 1.12 (0.60 to 2.08)	NA
IPC versus IPC	1 RCT	No	1 trial evaluated this outcome in total knees operated and showed OR 0.24 (0.05 to 1.08)	NA
IPC versus GCS	2 RCTs	No	1 trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.12 (0.01 to 1.99)	
▪ Limited to 2001-present	1 RCT (2 comp)	Yes	OR 0.12 (0.01 to 1.99)	NA
▪ Limited to THR	2 RCTs	No	1 trial showed RR 0.36 (0.13 to 1.00) while the second trial which compared enoxaparin plus IPC versus enoxaparin plus GCS showed OR 0.11 (0.002 to 5.78)	NA
▪ Limited to TKR	1 RCT	No	OR 0.14 (0.003 to 6.82)	NA
Distal DVT				
Enoxaparin versus other LMWH	1 RCT	No	RR 0.78 (0.46 to 1.34)	NA
IPC versus IPC	1 RCT	No	1 trial evaluated this outcome in total knees operated and showed RR 0.52 (0.29 to 0.93)	NA
IPC versus GCS	1 RCT (2 comp)	Yes	RR 0.07 (0.01 to 0.54)	NA
▪ Limited to 2001-present	1 RCT (2 comp)	Yes	RR 0.07 (0.01 to 0.54)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ Limited to THR	1 RCT (1 comp)	No	RR 0.15 (0.01 to 1.53)	NA
▪ Limited to TKR	1 RCT (1 comp)	No	RR 0.04 (0.004 to 0.33)	NA
Major Bleeding				
Enoxaparin versus other LMWH	2 RCT	Yes	RR 1.98 (0.53 to 7.37)	NA
▪ Limited to THR	1 RCT	No	OR 1.97 (0.20 to 19.25)	NA
▪ Limited to HFS	1 RCT	No	OR 1.98 (0.40 to 9.91)	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Major bleeding leading to reoperation				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Minor bleeding				
Enoxaparin versus other LMWH	1 RCT	No	OR 1.67 (0.84 to 3.36)	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Surgical site bleeding				
Enoxaparin versus other LMWH	2 RCT	Yes	RR 1.35 (0.30 to 5.97)	NA
▪ Limited to THR	1 RCT	No	OR 0.14 (0.003 to 6.82)	NA
▪ Limited to HFS	1 RCT	No	OR 1.98 (0.40 to 9.91)	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Bleeding leading to infection				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Bleeding leading to transfusion				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
HIT				

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Enoxaparin versus other LMWH	1 RCT	No	OR 7.48 (0.15 to 376.94)	NA
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Discomfort				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---
Readmission				
Enoxaparin versus other LMWH	0	---	---	--
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	--
Reoperation				
Enoxaparin versus other LMWH	0	---	---	---
IPC versus IPC	0	---	---	---
IPC versus GCS	0	---	---	---

*: All base case analyses are represented in this table. If only 1 trial was available subgroup analyses were not run. Only subgroup analyses with available data are represented in this table.

Abbreviations: comp=comparison(s); DVT=deep vein thrombosis; GCS=graduated compression stockings; HIT=heparin induced thrombocytopenia; HFS=hip fracture surgery; HRQOL=health related quality of life; IPC=intermittent pneumatic compression; LMWH=low molecular weight heparin; NA=Not Applicable; OBS=observational; OR=Peto's Odds Ratio; PE=pulmonary embolism; PTS=post thrombotic syndrome; RCT=Randomized Controlled Trial; RR=Relative Risk; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VKA=vitamin K antagonist; VTE=venous thromboembolism

Key Question 7

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

Key Points

- The strength of evidence for endpoints other than deep venous thrombosis evaluating the impact of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical prophylaxis was insufficient.
- There is moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of deep venous thrombosis versus pharmacologic prophylaxis alone in patients with major orthopedic surgery
    - The impact of pharmacological plus mechanical prophylaxis versus mechanical prophylaxis cannot be discerned due to a lack of events in experimental groups
- The use of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical does not significantly impact subclasses of deep venous thromboses (asymptomatic, proximal, or distal deep) in patients with major orthopedic surgery
- The use of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical does not significantly impact nonfatal pulmonary embolism, mortality, asymptomatic deep venous thrombosis, symptomatic deep venous thrombosis, proximal deep venous thrombosis, or distal deep venous thrombosis in patients with major orthopedic surgery
- The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis on major bleeding or minor bleeding could not be determined since no events occurred in the two comparative groups in the available trials.
    - No data is available to evaluate the comparative impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis on major bleeding or minor bleeding.
- No data is available to evaluate the comparative impact of two prophylactic strategies (pharmacologic plus mechanical) versus either pharmacologic or mechanical on symptomatically confirmed or major venous thromboembolism, postthrombotic syndrome, health related quality of life, major bleeding leading to reoperation, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, reoperation, or readmission in patients with major orthopedic surgery.

- The comparative impact of dual prophylactic modalities versus a single modality on fatal pulmonary embolism, or mortality due to bleeding could not be determined since no events occurred in the two comparative groups in the available trials.

Detailed Analysis

Study design and characteristics. Six randomized controlled trials (N = 995) and no controlled observation studies evaluated the impact of combined pharmacologic and mechanical modalities versus single modality on final health, intermediate and adverse outcomes.[107-110,126,127] All six trials were published as full text manuscripts. Four of the randomized controlled trials (N = 708) compared pharmacologic prophylaxis in combination with a mechanical prophylaxis versus pharmacologic prophylaxis alone,[107-109,126] one of the randomized controlled trials (N = 212) compared pharmacologic prophylaxis in combination with a mechanical prophylaxis versus mechanical prophylaxis alone,[110] and one randomized controlled trial (N = 75) included both comparisons.[127] Four trials enrolled exclusively patients who had total hip replacement surgery (N= 596),[108,110,126,127] one trial enrolled exclusively patients who had total knee replacement surgery (N=122),[109] and one trial enrolled both patient populations although reported results separately (N = 277).[107] No trials enrolled patients who had hip fracture surgery. The earliest trial was published in 1991 while the most recent published in 2008.[107,110] The duration of followup ranged from the postoperative period to 90 days. Two trials received funding from industry,[107,126] three trials were unfunded,[108-110] and one trial funding source was not reported.[127]
The mean age of enrolled patients ranged from 64 to years to 69.7 years. Females represented between 55.4 to 67.12 percent of the enrolled populations. The mean weight ranged from 71 to 88 kilograms with only one trial reporting obesity which ranged from 21.43 to 34.38 percent. Few patients enrolled had a history of venous thromboembolsim, with the majority of trials reporting 0 to 14 percent. Presence of varicosity was reported as 7 to 46.88 percent. The percent of patients with a history of malignancy ranged from 3.12 to 18.6 percent. None of the trials reported the percent of patients who had previously undergone orthopedic surgery.

Sixty-eight to 100 percent of patients underwent primary surgery and the number of patients who had cemented fixation during surgery ranged from 0 to 100 percent. Mean duration of surgery ranged from 86 to 125 minutes while the mean duration of anesthesia was not reported by any trial. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 12 to 100 percent of patients and regional anesthesia use ranging from 80 to 100 percent of patients. One trial specifically reported use of hypotensive regional anesthesia in all patients.[108] The mean length of hospital stay was infrequently reported, and when it was ranged from 3 to 10 days.

Outcome evaluations. A summary of the results is presented in

Table 14.

Symptomatic objectively confirmed venous thromboembolism. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Major venous thromboembolism. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.
Pulmonary embolism. Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on pulmonary embolism in patients who had major orthopedic surgery.[107,108] In the trial by Edwards and colleagues in 2008, patients who underwent total hip replacement or total knee replacement were enrolled and the outcomes are included separately for these two populations. All patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. No events occurred in the patients who had total hip replacement surgery and this analysis was not pooled with the others. The patients who had total knee replacement surgery in this study did provide data that could be pooled. In the second trial by Lieberman and colleagues in 1994, patients who had total hip replacement were randomized to receive aspirin plus intermittent pneumatic compression or aspirin alone. All patients also received elastic stockings. In the pooled analysis, in patients who received a combination of pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone the odds of pulmonary embolism were not significantly different [OR 1.03 (0.14 to 7.34)] (Appendix Figure 213). Statistical heterogeneity and publication bias could not be evaluated because there were too few strata.

Subgroup analyses were not possible in most instances. Limiting the analysis to trials comparing anticoagulant plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the trial by Edwards demonstrated no events in either group in those with total hip replacement and the odds of pulmonary embolism were not significantly different [OR 1.01 (0.06 to 16.35)] in patients who had total knee replacement. This is the same result obtained when limiting the original pooled analysis to trials published from 2001-present. In the trial by Lieberman and colleagues, which compared antiplatelet therapy plus mechanical prophylaxis versus antiplatelet therapy alone, the odds of pulmonary embolism were not significantly different [OR 1.04 (0.06 to 16.82)]. Only the total knee replacement analysis in the Edwards study provided data in that surgery type. In total hip replacement surgery, the evaluation in total hip replacement surgery by Edwards and colleagues had no events, and the study by Lieberman and colleagues found no significant effect. Subgroup analyses based on gender, age and ethnicity were not possible because no data was available.

One randomized controlled trial evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone on pulmonary embolism in patients who had major orthopedic surgery.[110] This trial by Woolson and colleagues enrolled patients who had total hip replacement and included two comparisons; aspirin plus intermittent pneumatic compression versus intermittent pneumatic compression alone and warfarin plus intermittent pneumatic compression versus intermittent pneumatic compression alone. No events occurred in either the experimental or control group in the warfarin comparison. In patients who received

antiplatelet therapy plus intermittent pneumatic compression versus intermittent pneumatic compression alone, the risk of pulmonary embolism was not significantly different [RR 1.57 (0.13 to 19.02)]. Subgroup analyses were possible since this was the only comparison available and data was not available to evaluate the effects of age, gender or ethnicity.

Fatal pulmonary embolism. Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on fatal pulmonary embolism in patients who had major orthopedic surgery.[107,108] However, no events occurred in the groups compared and therefore the risk of fatal pulmonary embolism could not be calculated.

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone in patients who had major orthopedic surgery.

Nonfatal pulmonary embolism. Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[107,108] The results obtained for all analyses of nonfatal pulmonary embolism are the same as those results and subgroup analyses reported for pulmonary embolism above, as all pulmonary embolism events were nonfatal (Appendix Figure 213).

No randomized controlled trials or controlled observational studies evaluated the impact of pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone in patients who had major orthopedic surgery.

Post thrombotic syndrome. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Mortality. Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on mortality in patients who had major orthopedic surgery although pooling of results was not possible.[107,108,127] The trial by Stannard and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling because the pharmacologic therapy was sequential in nature; additionally no events occurred in this trial. In the trial by Edwards and colleagues in 2008, patients who underwent total hip replacement or total knee replacement were enrolled and the outcomes are included separately for these two populations; however no events occurred in the groups compared. The remaining trial by Lieberman and colleagues in 1994 enrolled patients who had total hip replacement and were randomized to receive aspirin plus intermittent pneumatic compression or aspirin alone. In this trial, the odds of mortality were not significantly different in patients who received combination versus single modality prophylaxis [OR 7.72 (0.15 to 389.59)]. This is the same result obtained when evaluating the impact of pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis on mortality limited to total hip replacement, since the total hip replacement group in the trial by Edwards had no deaths, leaving

the trial by Lieberman and colleagues. The one trial which evaluated total knee replacement did not have any events,[107] and no trials evaluated patients who had hip fracture surgery. Subgroup analyses based on gender, age and ethnicity were not possible because no data was available to evaluate the effects of age, gender or ethnicity.

One randomized controlled trial evaluated the impact of combined pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone on mortality in patients who had major orthopedic surgery.[127] No deaths occurred in the groups compared therefore the risk of mortality could not be calculated.

Mortality due to bleeding. Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on mortality due to bleeding in patients who had major orthopedic surgery.[107,108,127] However, no events occurred in the groups compared and therefore the comparative risk of mortality due to bleeding could not be calculated.

One randomized controlled trial evaluated the impact of combined pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone on mortality due to bleeding in patients who had major orthopedic surgery.[127] No deaths due to bleeding occurred in the groups therefore the comparative risk of mortality could not be calculated.

Health related quality of life. No randomized controlled trials or controlled observational trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Deep vein thrombosis. Four randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[107,109,126,127] The trial by Stannard and colleagues enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling with the others because the administration of pharmacologic therapy was sequential in nature. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin), the risk of deep vein thrombosis was significantly decreased in patients who received combination prophylaxis versus single modality [RR 0.09 (0.01 to 0.85), NNT 5].

Of the trials amenable for pooling, the trial by Edwards and colleagues enrolled patients who underwent total hip replacement or total knee replacement and reported the results separately for these two populations. Patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. The trial by Kalodiki and colleagues enrolled patients who had total hip replacement surgery and randomized patients to receive either the combination of enoxaparin plus graduated compression stockings or enoxaparin alone. The fourth trial by Westrich and colleagues in 1996 enrolled patients who had total knee replacement surgery and randomized patients to receive either the combination of aspirin plus venous foot pump versus aspirin alone. In this trial, the number of deep vein thromboses was reported out of the number of operated knees because some patients had

bilateral surgery while others had unilateral surgery. We only used the unilateral data in pooled analyses. In pooled analysis of the Edwards, Kalodiki, and Westrich trials, patients who received pharmacologic prophylaxis plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of deep vein thrombosis was significantly decreased [RR 0.48 (0.32 to 0.72), NNT 3 to 67] (Appendix Figure 214).[107,109,126] Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.637).

When limiting this analysis to only anticoagulant agents combined with mechanical prophylaxis versus an anticoagulant agent alone, the trials by Edwards and Kalodiki and colleagues remained.[107,126] In patients who received anticoagulant prophylaxis plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.58 (0.32 to 1.06)] (Appendix Figure 215). Statistical heterogeneity was not detected (I^2 = 0 percent). In the single trial by Westrich and colleagues which compared antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone, in patients who received the combination versus monotherapy, the risk of deep vein thrombosis was significantly decreased [RR 0.40 (0.23 to 0.68), NNT 3].[109]

When limiting the original analysis to trials published from 2001-present, the two surgery populations from the trial by Edwards and colleagues remained.[107] In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.45 (0.16 to 1.26)] (Appendix Figure 216). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total hip replacement surgery, the trials by Edwards and Kalodiki remained.[107,126] In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone the risk of deep vein thrombosis was not significantly different [RR 0.64 (0.32 to 1.31)] (Appendix Figure 217). Statistical heterogeneity could not be evaluated because of too few strata. When limiting the original analysis to total knee replacement surgery the trials by Edwards and Westrich remained.[107,109] In patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone the risk of deep vein thrombosis was significantly decreased [RR 0.41 (0.25 to 0.68), NNT 3 to 18] (Appendix Figure 218). Statistical heterogeneity could not be evaluated because of too few strata. No trials evaluated patients who had hip fracture surgery and no data was available to evaluate the effects of age, gender or ethnicity.

The trial by Stannard and colleagues also compared pharmacologic prophylaxis plus mechanical prophylaxis versus mechanical prophylaxis alone.[127] However no events occurred in the groups compared therefore the risk of deep vein thrombosis could not be calculated.

Asymptomatic deep vein thrombosis. One randomized controlled trial by Stannard and colleagues in 1996 evaluated the impact of combination pharmacologic plus mechanical prophylaxis versus single modality prophylaxis on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[127] This trial enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone.

In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of asymptomatic deep vein

thrombosis was not significantly different in patients who received combination prophylaxis versus single modality [RR 0.20 (0.02 to 2.09)].

In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone, the risk of asymptomatic deep vein thrombosis could not be calculated because no events occurred. Subgroup analyses were not possible since only one trial was available.

Symptomatic deep vein thrombosis. One randomized controlled trial by Stannard and colleagues in 1996 evaluated the impact of combination pharmacologic plus mechanical prophylaxis versus single modality prophylaxis on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[127] This trial enrolled patients who had total hip replacement surgery and randomized patients to sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of symptomatic deep vein thrombosis was not significantly different in patients who received combination prophylaxis versus single modality [RR 0.14 (0.01 to 1.42)]. In the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone, the risk of symptomatic deep vein thrombosis could not be calculated because no events occurred. Subgroup analyses were not possible since only one trial was available.

Proximal deep vein thrombosis. Five randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on deep vein thrombosis in patients who had major orthopedic surgery.[107-109,126,127] The first trial by Edwards and colleagues in 2008 enrolled patients who had total hip or total knee replacement and reported the results separately for each surgery.[107] Patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. The second trial by Kalodiki and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive either the combination of enoxaparin plus graduated compression stockings or enoxaparin alone; however no events occurred in the groups compared, therefore this trial was excluded from the pooled analysis.[126] The third trial by Westrich and colleagues in 1996 enrolled patients who had total knee replacement surgery and randomized patients to receive either the combination of aspirin plus venous foot pump versus aspirin alone.[109] The fourth trial by Stannard and colleagues in 1996 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone.[127] This trial was not suitable for pooling because the sequential nature of the pharmacologic prophylaxis. In this trial, in the comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, the risk of proximal deep vein thrombosis was significantly decreased in patients who received combination prophylaxis versus single modality [RR 0.09 (0.01 to 0.85), NNT 5]. The fifth trial by Lieberman and colleagues enrolled patients who had total hip replacement

surgery and randomized patients to receive aspirin plus intermittent pneumatic compression or aspirin alone.[108] All patients also received elastic stockings. This trial was not suitable for pooling because the number of proximal deep vein thromboses was reported out of the total number of hips rather than patients. In this trial, the odds of proximal deep vein thrombosis were not significantly different in hip surgeries in which patients received combination versus single modality prophylaxis [OR 0.14 (0.003 to 6.93)]. In pooled analysis of the two remaining trials, in patients who received pharmacologic prophylaxis plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.33 (0.09 to 1.22)] (Appendix Figure 219).[109,126] Statistical heterogeneity and publication bias could not be evaluated because of too few strata.

When limiting this analysis to only anticoagulant agents combined with mechanical prophylaxis versus an anticoagulant agent alone, two trials remained although the trial by Edwards and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving the trial by Kalodiki and colleagues.[107,126] In this trial, in patients who received anticoagulant prophylaxis plus mechanical prophylaxis versus anticoagulant prophylaxis alone, the risk of deep vein thrombosis was not significantly different [RR 0.44 (0.15 to 1.30)]. In the single trial by Westrich and colleagues which compared antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone, in patients who received the combination versus monotherapy, the risk of proximal deep vein thrombosis was significantly decreased [RR 0.09 (0.01 to 0.84), NNT 8].

Subgroup analysis based on trials published from 2001-present was not possible because only the trial by Edwards and colleagues remained although no events occurred in either surgical population in the groups compared.[107] When limiting the original analysis to total hip replacement surgery, two trials remained although the trial by Edwards and colleagues was excluded from the analysis because no events occurred, leaving the trial by Kalodiki and colleagues. In this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.44 (0.15 to 1.30)].[126] When limiting the original analysis to total knee replacement surgery, two trials remained although the trial by Edwards and colleagues was excluded because no events occurred in the groups compared, leaving the trial by Westrich and colleagues. In this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.09 (0.01 to 1.51)].[109] Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this patient population and data was not reported in a way to evaluate the effects of age, gender or ethnicity.

Two randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus mechanical prophylaxis alone.[110,127] The comparison of sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump versus venous foot pump alone from the trial by Stannard and colleagues described above was not suitable for pooling because of the sequential nature of the pharmacologic therapy, additionally no events occurred in the groups compared.[127] The trial by Woolson and colleagues in 1991 enrolled patients who had total hip replacement surgery and randomized patients by hip (not patients since multiple surgeries in the same patient could have been randomized twice to different groups) to receive aspirin plus intermittent pneumatic compression, warfarin plus intermittent pneumatic compression, or intermittent pneumatic compression alone.[110] All patients also received graduated compression stockings. In the pooled

analysis of the two comparisons in this trial, in hip surgeries in which the patient received pharmacologic plus mechanical prophylaxis versus mechanical prophylaxis alone, the risk of proximal deep vein thrombosis was not significantly different [RR 0.78 (0.35 to 1.74)] (Appendix Figure 220). Statistical heterogeneity and publication bias could not be calculated because of too few strata. This is the same result obtained when limiting the original analysis to total hip replacement because the trial by Stannard and colleagues was ineligible for pooling, leaving the patients from Edwards and colleagues. When evaluating the two comparisons in this trial separately, the risk of proximal deep vein thrombosis was not significantly different in patients who received anticoagulant plus mechanical prophylaxis versus mechanical prophylaxis alone [RR 0.73 (0.28 to 1.88)] or in those who received antiplatelet plus mechanical prophylaxis versus mechanical prophylaxis alone [RR 0.82 (0.33 to 2.02)]. Subgroup analysis based on trial published from 2001-present or limited to total knee replacement or hip fracture surgery was not possible because no trials evaluated this patient population and data was not reported in a way to evaluate the effects of age, gender or ethnicity.

Distal deep vein thrombosis. Three randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on distal deep vein thrombosis in patients who had major orthopedic surgery.[107,108,127] The first trial by Stannard and colleagues in 1994 enrolled patients who had total hip replacement surgery and randomized patients to receive sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) plus venous foot pump, sequential pharmacologic prophylaxis (unfractionated heparin for three days then aspirin) alone, or venous foot pump alone. This trial was not suitable for pooling because the sequential nature of the pharmacologic prophylaxis, additionally no events occurred in the groups compared. The second trial by Lieberman and colleagues in 1994 enrolled patients who had total hip replacement surgery and randomized patients to receive aspirin plus intermittent pneumatic compression or aspirin alone. All patients also received elastic stockings. This trial was not suitable for pooling because the number of distal deep vein thromboses was reported out of the total number of hips rather than patients.[108] In this trial, the risk of distal deep vein thrombosis was not significantly different in hip surgeries in which patients received combination versus single modality prophylaxis [RR 0.89 (0.34 to 2.29)]. The third trial by Edwards and colleagues enrolled patients who underwent total hip replacement or total knee replacement and the outcomes are included separately for these two populations. All patients were randomized to receive either the combination of enoxaparin plus intermittent pneumatic compression or enoxaparin alone. In the pooled analysis of both groups in the trial by Edwards and colleagues, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis was not significantly different [RR 0.45 (0.16 to 1.26)] (Appendix Figure 221). This is the same result obtained when pooling trials published from 2001-present or when comparing anticoagulant plus mechanical prophylaxis versus anticoagulant prophylaxis alone (Appendix Figure 221). Statistical heterogeneity and publication bias could not be evaluated because of too few strata.

When limiting the pooled analysis to only patients who had total hip replacement surgery in this trial, in patients who received pharmacologic plus mechanical prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis were not significantly different [RR 0.46 (0.05 to 4.51)].[107] When limiting the analysis to only patients who had total knee replacement surgery in this trial, in patients who receive pharmacologic plus mechanical

prophylaxis versus pharmacologic prophylaxis alone, the risk of distal deep vein thrombosis was not significantly different [RR 0.45 (0.15 to 1.32)].[107] Only one trial compared aniplatelet plus mechanical prophylaxis versus mechanical prophylaxis alone.[108] In this trial, the risk of distal deep vein thrombosis was not significantly different in hip surgeries in which patients received antiplatelet plus mechanical prophylaxis versus antiplatelet prophylaxis alone [RR 0.89 (0.34 to 2.29)]. Subgroup analysis based on hip fracture surgery was not possible because no trials evaluated this population no data was available to evaluate the effects of age, gender or ethnicity.

The trial by Stannard and colleagues also compared pharmacologic prophylaxis plus mechanical prophylaxis versus mechanical prophylaxis alone.[127] However no events occurred in the groups compared therefore the risk of distal deep vein thrombosis could not be calculated.

Major bleeding. One randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on major bleeding in patients who had major orthopedic surgery however the risk of major bleeding could not be calculated because no events occurred in the groups compared.[109] Subgroup analyses were not possible because there was only one trial which evaluated this outcome and no data was available to evaluate the effects of age, gender or ethnicity.

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

Major bleeding leading to reoperation. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Minor bleeding. One randomized controlled trials evaluated the impact of combined pharmacologic and mechanical prophylaxis versus pharmacologic prophylaxis alone on minor bleeding in patients who had major orthopedic surgery however the risk of major bleeding could not be calculated because no events occurred in the groups compared.[109] Subgroup analyses were not possible because there was only one trial which evaluated this outcome and no data was available to evaluate the effects of age, gender or ethnicity.

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

Surgical site bleeding. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Bleeding leading to infection. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Bleeding leading to transfusion. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Heparin induced thrombocytopenia. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Discomfort. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.
Readmission. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Reoperation. No randomized controlled trials or controlled observational studies evaluated the impact of combined pharmacologic and mechanical prophylaxis versus single modality prophylaxis on this outcome in patients who had major orthopedic surgery.

Table 14. Summary of results for key question 7*

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Symptomatic objectively confirmed VTE				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Major VTE				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
PE				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	OR 1.03 (0.14 to 7.34)	NA
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
▪ Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
▪ 2001-present	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
▪ THR	2 RCTs	No	1 RCT had no events; the other showed an OR 1.04 (0.06 to 16.82)	NA
▪ TKR	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT (2 comp)	No	1 comparison had no events; the other showed a RR 1.57 (0.13 to 19.02)	NA
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (1comp)	No	No events occurred in the groups compared	NA
▪ Antiplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT(1 comp)	No	RR 1.57 (0.13 to 19.02)	NA
▪ THR	1 RCT (2 comp)	No	1 comparison had no events; the other showed a RR 1.57 (0.13 to 19.02)	
Fatal PE				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	No	No events occurred in the groups compared	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
Nonfatal PE				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	OR 1.03 (0.14 to 7.34)	NA
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
▪ 2001-present	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
▪ THR	1 RCT	No	OR 1.04 (0.06 to 16.82)	NA
▪ TKR	1 RCT	No	OR 1.01 (0.06 to 16.35)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
PTS				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Mortality				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	No	2 RCTs had no events in the groups compared; the third showed an OR of 7.72 (0.15 to 389.50)	NA
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	No	No events occurred in the groups compared	NA
▪ Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	OR 7.72 (0.15 to 389.50)	NA
▪ 2001-present	1 RCT	No	No events in the groups compared	NA
▪ THR	2 RCTs	No	1 RCT had no events; the third showed an OR 7.72 (0.15 to 389.50)	NA
▪ TKR	1 RCT	No	No events in the groups compared	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Mortality due to bleeding				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	No	No events occurred in the groups compared	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
HRQOL				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
DVT				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	4 RCTs	Yes	RR 0.48 (0.32 to 0.72)	0
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	Yes	RR 0.58 (0.32 to 1.06)	0

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.40 (0.23 to 0.68)	NA
▪ 2001-present	1 RCT (2 comp)	Yes	RR 0.45 (0.16 to 1.26)	NA
▪ THR	2 RCTs	Yes	RR 0.64 (0.32 to 1.31)	NA
▪ TKR	2 RCTs	Yes	RR 0.41 (0.25 to 0.68)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Asymptomatic DVT				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	RR 0.20 (0.02 to 2.09)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Symptomatic DVT				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	RR 0.14 (0.01 to 1.42)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Proximal DVT				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	3 RCTs	Yes	RR 0.33 (0.09 to 1.22)	NA
	2 RCTs	No	Two trials ineligible for pooling were evaluated separately and showed OR 0.14 (0.003 to 6.93) in 1 trial and RR 0.09 (0.01 to 0.85) in the other trial	
Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.44 (0.15 to 1.30)	NA
Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.09 (0.01 to 0.84)	NA
▪ 2001-present	1 RCT (2 comp)	No	No events occurred in the groups compared	NA
▪ THR	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.44 (0.15 to 1.30)	NA
▪ TKR	2 RCTs	No	1 RCT had no events; 1 RCT showed RR 0.09 (0.01 to 1.51)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	2 RCTs	Yes	RR 0.78 (0.35 to 1.74)	NA
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (1 comp)	No	RR 0.73 (0.28 to 1.88)	NA
▪ Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT (1 comp)	No	RR 0.82 (0.33 to 2.02)	NA

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ THR	2 RCTs	Yes	1 RCT was ineligible for pooling; the remaining RCT had 2 comparisons pooled to show a RR 0.78 (0.35 to 1.74)	NA
Distal DVT				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	2 RCTs	Yes	No significant difference, one trial had no events and the remaining trial had two comparisons which were pooled to show RR 0.45 (0.16 to 1.26)	NA
	1 RCT	No	One trial ineligible for pooling showed RR 0.89 (0.34 to 2.29)	
▪ Anticoagulant + mechanical prophylaxis versus anticoagulant prophylaxis	1 RCT (2 comp)	Yes	RR 0.60 (0.23 to 1.59)	NA
▪ Anitplatelet + mechanical prophylaxis versus antiplatelet prophylaxis	1 RCT	No	RR 0.89 (0.34 to 2.29)	NA
▪ 2001-present	1 RCT (2 comp)	Yes	RR 0.60 (0.23 to 1.59)	NA
▪ THR	3 RCTs	Yes	2 RCTs were ineligible for pooling; the remaining RCT had 2 comparisons when pooled showed a RR 0.60 (0.23 to 1.59)	NA
▪ TKR	1 RCT	No	RR 0.45 (0.15 to 1.32)	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Major Bleeding				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
Major Bleeding Leading to Reoperation				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Minor Bleeding				
Pharmacologic + mechanical prophylaxis versus pharmacologic prophylaxis	1 RCT	No	No events occurred in the groups compared	NA
Pharmacologic + mechanical prophylaxis versus mechanical prophylaxis	0	---	---	---
Surgical Site Bleeding				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Bleeding Leading to Infection				

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Bleeding Leading to Transfusion				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
HIT				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Discomfort				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Redmission				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---
Reoperation				
Pharmacologic + mechanical prophylaxis versus single modality	0	---	---	---

* All base case analyses are represented in this table. If only one trial was available in a base case analysis no subgroups analyses were performed and therefore are not represented in this table. Only subgroup analyses with trials or studies are represented in this table.

Abbreviations: DVT=deep vein thrombosis; HRQOL=health related quality of life; NA=Not Applicable; OR=Peto's Odds Ratio; PE=pulmonary embolism; PTS=post thrombotic syndrome; RCT=Randomized Controlled Trial; RR=Relative Risk; VTE=venous thromboembolism

Key Question 8

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

Key Points

- In this key question, the impact of prolonging prophylaxis for 28 days or longer on events was compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of symptomatic objectively confirmed venous thromboembolism versus shorter term prophylaxis. While higher heterogeneity was found, the direction of effect was consistent between all of the trials.
    - In subgroup analyses of trials conducted from 2001 to the present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis reduces the occurrence of symptomatic objectively confirmed venous thromboembolism versus shorter term prophylaxis.
    - In the one trials that stratified results based on gender, women with total hip and total knee replacement surgery had fewer symptomatic venous thromboembolism events after prolonged prophylaxis as did men with total hip replacement.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of pulmonary embolism versus shorter term prophylaxis.
    - In subgroup analyses of trials conducted from 2001 to the present or in patients undergoing total hip replacement surgery, prolonged prophylaxis reduces the occurrence of pulmonary embolism versus shorter term prophylaxis.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of nonfatal pulmonary embolism versus shorter term prophylaxis.
    - In subgroup analyses of trials conducted from 2001 to the present or in patients undergoing total hip replacement surgery, prolonged prophylaxis reduces the occurrence of nonfatal pulmonary embolism versus shorter term prophylaxis.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of deep venous thrombosis versus shorter term prophylaxis. While higher heterogeneity was found, the direction of effect was consistent between all of the trials.
    - In subgroup analyses of trials conducted from 2001 to the present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis reduces the occurrence of deep venous thrombosis versus shorter term prophylaxis.

- In the base case analysis, prolonged prophylaxis reduces the occurrence of asymptomatic deep venous thrombosis versus shorter term prophylaxis.
    - In subgroup analyses of patients undergoing total hip replacement surgery, prolonged prophylaxis reduces the occurrence of deep venous thrombosis versus shorter term prophylaxis.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of symptomatic deep venous thrombosis versus shorter term prophylaxis.
- In the base case analysis, prolonged prophylaxis reduces the occurrence of proximal deep venous thrombosis versus shorter term prophylaxis.
    - In subgroup analyses of trials conducted from 2001 to the present or in patients undergoing total hip replacement or hip fracture surgery, prolonged prophylaxis reduces the occurrence of proximal deep venous thrombosis versus shorter term prophylaxis.
- While no differences were seen in the base case analysis, prolonged prophylaxis reduces the occurrence of distal deep venous thrombosis versus shorter term prophylaxis in hip fracture surgery.
- In the base case analysis, prolonged prophylaxis increases the occurrence of minor bleeding versus shorter term prophylaxis.
    - In subgroup analyses patients undergoing total hip replacement prolonged prophylaxis increases the occurrence of minor bleeding versus shorter term prophylaxis.
- In the base case analysis, prolonged prophylaxis increases the occurrence of surgical site bleeding versus shorter term prophylaxis.
    - In subgroup analyses of trials conducted from 2001 to the present or patients undergoing hip fracture surgery, prolonged prophylaxis increases the occurrence of surgical site bleeding versus shorter term prophylaxis.
- While no significant difference was seen in the base case analysis, prolonged prophylaxis reduced the occurrence of hospital readmission versus shorter term prophylaxis in total hip replacement surgery.

Detailed Analysis

Study design and characteristics. Eight randomized controlled trials (N=2917) and no controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on final, intermediate, or adverse outcomes [111,114,115,117,119,120,124,188] All trials were published as full text manuscripts. Six trials (N=1388) enrolled exclusively patients who had total hip replacement surgery.[111,115,119,120,124,188] One trial (N=873) enrolled patients who had either total hip replacement or total knee replacement surgery and reported the results separately for each surgical population.[114] One trial (N=656) enrolled patients who had hip fracture surgery.[117]

One trial (N=656) evaluated the factor Xa inhibitor fondaparinux,[117] one trial (N=360) evaluated the vitamin K antagonist warfarin,[124] and five trials (N=1636) evaluated injectable low molecular weight heparin agents including enoxparin and dalteparin.[111,114,119,120,188] One trial (N=265) compared dalteparin prophylaxis for 7 days versus dalteparin prophylaxis for 35 days but patients also received dextran and graduated compression stockings as part of the randomized prophylaxis regimen therefore this trial was not pooled with other trials and is evaluated separately in this key question.[115] The earliest trial was published in 1997 while the

most recent was published in 2003. The duration of followup ranged from 32 to 90 days. Three trials were funded by industry,[114,117,120] one trial was funded by government/foundation,[111] and the remaining trials did not disclose the funding source.

The mean age of enrolled patients ranged from 63.4 years to 79 years. Females represented between 38.2 and 73.6 percent of the enrolled populations. The mean weight ranged from 65 to 89.2 kilograms and obesity ranged from 7.8 to 75.1percent. Few patients enrolled had a history of venous thromboembolism ranging from 1.12 to 9.0 percent. Presence of varicosity ranged from 7.6 to 24 percent. The percent of patients with a history of malignancy ranged from 1.7 to 9.4 percent. Few trials reported the percent of patients who had previously undergone orthopedic surgery ranging from 3.6 to 13.33 percent.

Seventy-two to 100 percent of patients underwent primary surgery and the percent of patients who had cemented fixation during surgery ranged from 23.9 to 84.1 percent. Mean duration of surgery ranged from 95 to 114 minutes and the mean duration of anesthesia was reported by two trials with a range of 125.83 to 165 minutes. Use of general versus regional anesthesia varied, with general anesthesia use ranging from 0.88 to 97.2 percent of patients and regional anesthesia use ranging from 25.0 to 99.12 percent of patients. The mean length of hospital stay was reported by one trial, and it was 9 days.

Outcome evaluations. A summary of the results is presented in

Table 15**.**

Symptomatic objectively confirmed venous thromboembolism. Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on symptomatic objectively confirmed venous thromboembolism in patients who had major orthopedic surgery.[114,117,119,124] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement surgery).[114] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.38 (0.19 to 0.77), NNT 8 to 54] (Appendix Figure 222). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 69.1 percent, Egger's p-value = 0.150). The direction of effect was the same in all of the trials and differed only in the magnitude of the effect. Some of the heterogeneity may be related to the type of surgery.

When limiting the original analysis to trials published from 2001-present three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.[114,117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.43 (0.20 to 0.89), NNT 8 to 59] (Appendix Figure 223). A higher level of statistical heterogeneity was detected (I^2 = 72.9 percent). When limiting the original analysis to total hip replacement surgery three trials remained.[114,119,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.33 (0.21 to 0.51), NNT 7 to 30] (Appendix Figure 224). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was not significantly different [RR 0.84 (0.57 to 1.23)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of symptomatic objectively confirmed venous thromboembolism was significantly decreased [RR 0.11 (0.02 to 0.68), NNT 38].

The trial by Comp and colleagues evaluated the impact of gender on the efficacy of extended duration prophylaxis versus standard duration prophylaxis on symptomatic venous thromboembolism in patients who had major orthopedic surgery.[114] Two surgical populations were evaluated separately in this trial; total hip replacement and total knee replacement surgery. In males, extended duration prophylaxis significantly reduced the percent of patients who had symptomatic venous thromboembolism compared to standard duration prophylaxis in patients who had total hip replacement (6.3 percent versus 23.6, $p < 0.001$) but not in those who had total knee replacement (23.6 percent versus 15.3 percent, $p = 0.211$). In females extended duration prophylaxis significantly reduced the percent of patients who had symptomatic venous thromboembolism compared to standard duration prophylaxis in patients who had total hip replacement (9.7 percent versus 22.9, $p = 0.014$) and in those who had total knee replacement (13.3 percent versus 25.2 percent, $p = 0.025$).

Major venous thromboembolism. One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on major venous thromboembolism in patients who had major orthopedic surgery.[124] This trial by Prandoni and colleagues in 2002 evaluated patients who had total hip replacement surgery and received warfarin prophylaxis for 28 days versus warfarin prophylaxis until hospital discharge, with a mean hospital length of stay of 9 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major venous thromboembolism were not significantly different [OR 0.34 (0.11 to 1.07)]. Subgroup analyses were not possible as only one trial with events was available.

Pulmonary embolism. Seven randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on pulmonary embolism in patients who had major orthopedic surgery.[111,114,115,117,119,120,124] The trial by Comp and colleagues included two separate comparisons based on the surgery type; total hip replacement and total knee replacement surgery and the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.[114,120] The trial by Dahl and colleagues was evaluated separately from the pooled analysis because patients received triple prophylaxis.[115] The remaining five trials were pooled and in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.14 (0.04 to 0.47), NNT 24 to 232] (Appendix Figure 225). Statistical heterogeneity and publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.471).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.54 (0.16 to 1.80)].

When limiting the original analysis to trials published from 2001-present three trials remained, with the trial by Comp and colleagues including two separate comparisons based on surgery type.[114,117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.59), NNT 9 to 232] (Appendix Figure 226). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total hip replacement surgery five trials remained although the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.[111,114,119,120,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were significantly decreased [OR 0.13 (0.02 to 0.77), NNT 24] (Appendix Figure 227). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.20)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of pulmonary embolism were not significantly different [OR 0.14 (0.01 to 1.31)].

Fatal pulmonary embolism. Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on fatal pulmonary embolism in patients who had major orthopedic surgery.[114,115,117,119,120,124] Four trials were excluded from the analysis because no events occurred. The trial by Dahl and colleagues was evaluated separately because patients received triple prophylactic therapy.[115] The remaining trial by Eriksson and colleagues in 2003 evaluated patients who had hip fracture surgery and who received fondaparinux prophylaxis for 25 to 31 days versus fondaparinux prophylaxis fro 6 to 8 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of fatal pulmonary embolism were not significantly different [OR 0.14 (0.003 to 6.90)]. Subgroup analyses were not possible as only one trial with events was available.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial the odds of fatal pulmonary embolism were not significantly different [OR 0.13 (0.003 to 6.51)] in patients who received prolonged prophylaxis versus shorter duration prophylaxis.

Nonfatal pulmonary embolism. Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on nonfatal pulmonary embolism in patients who had major orthopedic surgery.[114,115,117,119,120,124] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement surgery) and the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.[114,120] The trial by Dahl and colleagues was evaluated separately from the pooled analysis because patients received triple prophylactic therapy.[115] The four remaining trials were pooled and in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.54), NNT 58] (Appendix Figure 228). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected although the presence of publication bias was detected (I^2 = 0 percent, Egger's p-value = 0.016).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial the odds of nonfatal pulmonary embolism were not significantly different [OR 0.13 (0.01 to 2.06)] in patients who received prolonged prophylaxis versus shorter duration prophylaxis.

When limiting the original analysis to trials published from 2001-present, three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.[114,117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.03 to 0.66), NNT 9 to 232] (Appendix Figure 229). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total hip replacement surgery four trials remained although the trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared.[114,119,120,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of nonfatal pulmonary embolism were significantly decreased [OR 0.13 (0.02 to 0.93), NNT 58] (Appendix Figure 230). A range for the number needed to treat could not be calculated because the lowest control event rate was zero. Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original

analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.20)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, the odds of nonfatal pulmonary embolism were not significantly different [OR 0.14 (0.01 to 2.19)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

Post thrombotic syndrome. No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Mortality. Six randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on mortality in patients who had major orthopedic surgery.[114,115,117,119,120,124] The trial by Dahl and colleagues was evaluated separately because patients received triple prophylactic therapy.[115] Four trials were excluded from the analysis because no events occurred, leaving the trial by Eriksson and colleagues in 2003. This trial evaluated patients who had hip fracture surgery and received fondaparinux prophylaxis for 25 to 31 days versus fondaparinux prophylaxis for 6 to 8 days. In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of mortality were not significantly different [OR 0.75 (0.26 to 2.17)]. Subgroup analyses were not possible as only one trial with events was available.

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial the risk of mortality was not significantly different [RR 0.98 (0.10 to 9.31)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

Mortality due to bleeding. Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on mortality due to bleeding in patients who had major orthopedic surgery however no events occurred in the groups compared therefore the risk of mortality due to bleeding could not be calculated.[114,115,119,120,124]

Health related quality of life. No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Deep vein thrombosis. Eight randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on deep vein thrombosis in patients who had major orthopedic surgery.[111,114,115,117,119,120,124,188] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).[114] The trial by Dahl and colleagues was evaluated separately from the analysis because patients received triple prophylactic therapy.[115] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.37 (0.21 to 0.64), NNT 5 to 32] (Appendix Figure

231). A higher level of statistical heterogeneity was detected but the presence of publication bias was not detected (I^2 = 78.3 percent, Egger's p-value = 0.164).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.61 (0.38 to 0.97)].

When limiting the original analysis to trials published from 2001-present three trials remained with the trial by Comp and colleagues including two separate comparisons based on surgery type.[114,117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.28 (0.09 to 0.87), NNT 5 to 28] (Appendix Figure 232). A higher level of statistical heterogeneity was detected (I^2 = 90.9 percent). When limiting the original analysis to total hip replacement surgery six trials remained.[111,114,119,120,124,188] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.41 (0.31 to 0.55), NNT 6 to 34] (Appendix Figure 233). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was not significantly different [RR 0.84 (0.57 to 1.23)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of deep vein thrombosis was significantly decreased [RR 0.04 (0.01 to 0.12), NNT 4].

Asymptomatic deep vein thrombosis. Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on asymptomatic deep vein thrombosis in patients who had major orthopedic surgery.[111,119,124,188] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of asymptomatic deep venous thrombosis was significantly decreased [RR 0.48 (0.31 to 0.75), NNT 8 to 65] (Appendix Figure 234). Statistical heterogeneity and the presence of publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.252). This is the same result obtained when limiting the analysis to total hip replacement surgery since all four trials evaluated this surgical population. When limiting the original analysis to trials published from 2001-present, one trial remained.[124] In this trial, the odds of asymptomatic deep vein thrombosis were not significantly different [OR 0.25 (0.05 to 1.24)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. Subgroup analysis based on total knee replacement or hip fracture surgery were not possible since no trials evaluated these surgical populations.

Symptomatic deep vein thrombosis. Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on symptomatic deep vein thrombosis in patients who had major orthopedic surgery.[111,115,117,119,124] The trial by Dahl and colleagues was evaluated separately because patients received triple prophylactic therapy.[115] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were significantly decreased [OR 0.36 (0.16 to 0.81), NNT 27 to 79] (Appendix Figure 235). Statistical heterogeneity and the presence of publication bias were not detected (I^2 = 0 percent, Egger's p-value = 0.155).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 1.83 (0.57 to 5.87)].

When limiting the original analysis to trials published from 2001-present, two trials remained.[117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.36 (0.12 to 1.12)] (Appendix Figure 236). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery three trials remained.[111,119,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.43 (0.16 to 1.12)] (Appendix Figure 237). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to hip fracture surgery one trial remained.[117] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of symptomatic deep vein thrombosis were not significantly different [OR 0.24 (0.05 to 1.06)]. Subgroup analysis based on hip fracture surgery was not possible as no trials evaluated this surgical population.

Proximal deep vein thrombosis. Seven randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on proximal deep vein thrombosis in patients who had major orthopedic surgery.[114,115,117,119,120,124,188] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).[114] The trial by Dahl and colleagues was evaluated separately from the analysis because patients received triple prophylactic therapy.[115] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.29 (0.16 to 0.52), NNT 9 to 71] (Appendix Figure 238). A lower level of statistical heterogeneity was detected and the presence of publication bias was not detected (I^2 = 48.1 percent, Egger's p-value = 0.507).

The trial by Dahl and colleagues randomized patients who had total hip replacement surgery to continue dalteparin for a total of 35 days versus placebo until day 35 after seven days of prophylaxis with dalteparin, dextran, and graduated compression stockings.[115] In this trial the risk of proximal deep vein thrombosis was not significantly different [RR 0.65 (0.31 to 1.38)] in patients who received prolonged prophylaxis versus standard duration prophylaxis.

When limiting the original analysis to trials published from 2001-present, three trials remained.[114,117,124] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.23 (0.08 to 0.61), NNT 8 to 57] (Appendix Figure 239). A higher level of statistical heterogeneity was detected (I^2 = 65.5 percent). When limiting the original analysis to total hip replacement surgery five trials remained.[114,119,120,124,188] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.30 (0.19 to 0.49), NNT 7 to 72] (Appendix Figure 240). Statistical heterogeneity was not detected (I^2 = 0 percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration

prophylaxis the risk of proximal deep vein thrombosis was not significantly different [RR 0.54 (0.25 to 1.16)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of proximal deep vein thrombosis was significantly decreased [RR 0.06 (0.02 to 0.21), NNT 7].

Distal deep vein thrombosis. Four randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on distal deep vein thrombosis in patients who had major orthopedic surgery.[114,117,119,120] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).[114] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.39 (0.15 to 1.04)] (Appendix Figure 241). A higher statistical heterogeneity was detected as was the presence of publication bias (I^2 =83.6 percent, Egger's p-value = 0.023).

When limiting the original analysis to trials published from 2001-present, two trials remained with the trial by Comp and colleagues contributing two separate comparisons.[114,117] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.33 (0.07 to 1.51)] (Appendix Figure 242). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total hip replacement surgery three trials remained.[114,119,120] In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 0.53 (0.24 to 1.17)] (Appendix Figure 243). A higher level of statistical heterogeneity was detected (I^2 = 53.4 percent). When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was not significantly different [RR 1.09 (0.67 to 1.78)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of distal deep vein thrombosis was significantly decreased [RR 0.02 (0.004 to 0.14), NNT 6].

Major bleeding. Five randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on major bleeding in patients who had major orthopedic surgery.[114,117,120,124,188] The trial by Comp and colleagues included two separate comparisons based on the surgery type (total hip replacement and total knee replacement).[114] One trial and one comparison in total hip replacement surgery by Comp and colleagues were excluded from the analysis because no events occurred in the groups compared.[114,120] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 2.18 (0.73 to 6.51)] (Appendix Figure 244). A lower statistical heterogeneity was detected and the presence of publication bias was not detected (I^2 = 35.6 percent, Egger's p-value = 0.334).

When limiting the original analysis to trials published from 2001-present, three trials remained with the trial by Comp and colleagues contributing two separate comparisons.[114,117,124] The comparison in total hip replacement surgery by Comp and colleagues was excluded from the analysis because no events occurred in the groups compared. In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not

significantly different [OR 2.76 (0.88 to 8.61)] (Appendix Figure 245). A lower level of statistical heterogeneity was detected (I^2 =22.3 percent). When limiting the original analysis to total hip replacement surgery four trials remained.[114,120,124,188] Two trials were excluded from the analysis because no events occurred in the groups compared.[114,120] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 0.98 (0.06 to 15.70)] (Appendix Figure 246). Statistical heterogeneity could not be evaluated because of too few studies. When limiting the original analysis to total knee replacement surgery one comparison from the trial by Comp and colleagues remained.[114] In this comparison, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 0.14 (0.003 to 6.95)]. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding were not significantly different [OR 3.40 (0.98 to 11.84)].

Major bleeding leading to reoperation. One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on major bleeding leading to reoperation in patients who had major orthopedic surgery.[117] In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of major bleeding leading to reoperation were not significantly different [OR 1.01 (0.14 to 7.18)]. Subgroup analysis was not possible because there was only one study available.

Minor bleeding. Three randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on minor bleeding in patients who had major orthopedic surgery.[117,120,188] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were significantly increased [OR 2.44 (1.41 to 4.20), NNH 11 to 118] (Appendix Figure 247). Statistical heterogeneity was not detected while publication bias not could be evaluated because of too few studies (I^2 =0 percent).

When limiting the original analysis to trials published from 2001-present, one trial remained.[117] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were not significantly different [OR 2.39 (0.54 to 10.59)]. When limiting the original analysis to total hip replacement surgery two trials remained.[120,188] In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were significantly increased [OR 2.44 (1.36 to 4.39), NNH 11 to 20] (Appendix Figure 248). Statistical heterogeneity could not be evaluated because of too few studies. Subgroup analysis based on total knee replacement surgery could not be evaluated because no trials evaluated this surgical population. When limiting the original analysis to hip fracture surgery one trial remained.[117] In this trial, in patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of minor bleeding were not significantly different [OR 2.39 (0.54 to 10.59)].

Surgical site bleeding. One randomized controlled trial evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on surgical site

bleeding in patients who had major orthopedic surgery.[117] In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In patients who received prolonged prophylaxis versus standard duration prophylaxis the odds of surgical site bleeding were significantly increased [OR 7.55 (1.51 to 37.64)]. The number needed to harm could not be calculated because the control event rate was zero. Subgroup analysis was not possible because there was only one study available.

Bleeding leading to infection. No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Bleeding leading to transfusion. Two randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on bleeding leading to transfusion in patients who had major orthopedic surgery.[117,120] One trial by Planes and colleagues was excluded from the analysis because no events occurred in the groups compared, leaving one trial for the analysis. In this trial by Eriksson and colleagues in 2003, patients who had hip fracture surgery were randomized to receive either fondaparinux prophylaxis for 25 to 31 days or fondaparinux prophylaxis for 6 to 8 days after surgery. In this trial, the risk of bleeding leading to transfusion was not significantly different [RR 1.46 (0.85 to 2.51)] in patients who received prolonged prophylaxis versus standard duration prophylaxis. Subgroup analyses were not possible since only one trial with events was available.

Heparin induced thrombocytopenia. No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Discomfort. No randomized controlled trials or controlled observational studies evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery on this outcome.

Readmission. One randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on readmission in patients who had major orthopedic surgery.[114] This trial by Comp and colleagues in 2001 included two separate comparisons based on the surgery type (total hip replacement and total knee replacement). When pooling these two comparisons, in patients who had major orthopedic surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of readmission was not significantly different [RR 0.29 (0.06 to 1.34)] (Appendix Figure 249). Patients were randomized to receive enoxaparin prophylaxis for 7 to 10 days versus enoxaparin prophylaxis for 28 to 31 days. In patients who had total hip replacement surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of readmission was significantly decreased [RR 0.13 (0.04 to 0.39), NNT 12 to 23]. In patients who had total knee replacement surgery and received prolonged prophylaxis versus standard duration prophylaxis the risk of readmission was not significantly different [RR 0.59 (0.24 to 1.44)]. Subgroup analyses based on hip fracture surgery was not possible since no trials evaluated this surgical population.

Reoperation. One randomized controlled trials evaluated the effect of prolonging prophylaxis for 28 days or longer compared to prophylaxis for 7 to 10 days on reoperation in patients who had major orthopedic surgery.[111] This trial by Andersen and colleagues in 1997 evaluated patients who had total hip replacement surgery and received dalteparin prophylaxis for 5 to 7 days versus dalteparin prophylaxis for 35 days. In patients who received prolonged prophylaxis versus standard duration prophylaxis the risk of reoperation was not significantly different [RR 0.21 (0.02 to 2.16)]. Subgroup analyses were not possible as only one trial was available.

Table 15. Summary of results for key question 8*

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Symptomatic objectively confirmed VTE				
Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.38 (0.19 to 0.77)	69.1
▪ 2001-present	3 RCTs	Yes	RR 0.43 (0.20 to 0.89)	72.9
▪ THR	3 RCTs	Yes	RR 0.33 (0.21 to 0.51)	0
▪ TKR	1 RCT (1 comp)	No	RR 0.84 (0.57 to 1.23)	NA
▪ HFS	1 RCT	No	RR 0.11 (0.02 to 0.68)	NA
▪ Age, gender, ethnicity	1 RCT	No	RCT showed that extended duration prophylaxis significantly reduced the percent of patients with symptomatic venous thromboembolism in males and in females undergoing THR and in females undergoing TKR. In males undergoing TKR, there was no significant difference in the percent of patients with symptomatic venous thromboembolism	NA
Major VTE				
Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 0.34 (0.11 to 1.07)	NA
PE				
Prolonged prophylaxis versus standard duration prophylaxis	6 RCTs	Yes	OR 0.14 (0.04 to 0.47)	0
	1 RCT	No	One trial ineligible for pooling showed OR 0.54 (0.16 to 1.80)	NA
▪ 2001-present	3 RCTs	Yes	OR 0.13 (0.03 to 0.59)	0
▪ THR	5 RCTs	Yes	OR 0.13 (0.02 to 0.77)	0
▪ TKR	1 RCT (1 comp)	No	OR 0.14 (0.01 to 2.20)	NA
▪ HFS	1 RCT	No	OR 0.14 (0.01 to 1.31)	NA
Fatal PE				
Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	Four trials had no events; remaining trial showed OR 0.14 (0.003 to 6.90)	NA
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.003 to 6.51)	NA
▪ 2001-present	3 RCTs	No	Two trials had no events; remaining trial showed OR 0.14 (0.003 to 6.90)	NA
▪ THR	5 RCTs	No	Four trials had no events; one trial ineligible for pooling showed OR 0.13 (0.003 to 6.51)	NA
▪ HFS	1 RCT	No	OR 0.14 (0.003 to 6.90)	NA
Nonfatal PE				

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	OR 0.13 (0.03 to 0.54)	0
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)	NA
▪ 2001-present	3 RCTs	Yes	OR 0.13 (0.03 to 0.66)	0
▪ THR	4 RCTs	Yes	OR 0.13 (0.02 to 0.93)	0
	1 RCT	No	One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06)	NA
▪ TKR	1 RCT (1 comp)	No	OR 0.14 (0.01 to 2.20)	NA
▪ HFS	1 RCT	No	OR 0.14 (0.01 to 2.19)	NA
PTS				
Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Mortality				
Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	No	Four trials had no events; remaining trial showed OR 0.75 (0.26 to 2.17)	NA
	1 RCT	No	One trial ineligible for pooling showed RR 0.98 (0.10 to 9.31)	NA
▪ 2001-present	3 RCTs	No	2 trials were excluded from the analysis because no events occurred in the groups compared; remaining trial showed OR 0.75 (0.26 to 2.17)	NA
▪ THR	4 RCTs	No	3 trials were excluded from the analysis because no events occurred in the groups compared; one trial ineligible for pooling showed RR 0.98 (0.10 to 9.31)	NA
▪ TKR	1 RCT	No	No events occurred in the groups compared	NA
▪ HFS	1 RCT	No	OR 0.75 (0.26 to 2.17)	NA
Mortality due to bleeding				
Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	No	No events occurred in the groups compared	NA
▪ 2001-present	2 RCTs	No	No events occurred in the groups compared	NA
▪ THR	5 RCTs	No	No events occurred in the groups compared	NA
▪ TKR	1 RCT	No	No events occurred in the groups compared	NA
HRQOL				
Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
DVT				
Prolonged prophylaxis versus standard duration prophylaxis	7 RCTs	Yes	RR 0.37 (0.21 to 0.64)	78.3
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)	NA
▪ 2001-present	3 RCTs	Yes	RR 0.28 (0.09 to 0.87)	90.9

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
▪ THR	6 RCTs	Yes	RR 0.41 (0.31 to 0.55)	0
	1 RCT	No	One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97)	NA
▪ TKR	1 RCT	No	RR 0.84 (0.57 to 1.23)	NA
▪ HFS	1 RCT	No	RR 0.04 (0.01 to 0.12)	NA
Asymptomatic DVT				
Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.48 (0.31 to 0.75)	0
▪ 2001-present	1 RCT	No	OR 0.25 (0.05 to 1.24)	NA
▪ THR	4 RCTs	Yes	RR 0.48 (0.31 to 0.75)	0
Symptomatic DVT				
Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	OR 0.36 (0.16 to 0.81)	0
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)	NA
▪ 2001-present	2 RCTs	Yes	OR 0.36 (0.12 to 1.12)	NA
▪ THR	4 RCTs	Yes	OR 0.43 (0.16 to 1.12)	0
	1 RCT	No	One trial ineligible for pooling showed OR 1.83 (0.57 to 5.87)	NA
▪ HFS	1 RCT	No	OR 0.24 (0.05 to 1.06)	NA
Proximal DVT				
Prolonged prophylaxis versus standard duration prophylaxis	6 RCTs	Yes	RR 0.29 (0.16 to 0.52)	48.1
	1 RCT		One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)	NA
▪ 2001-present	3 RCTs	Yes	RR 0.23 (0.08 to 0.61)	65.5
▪ THR	5 RCTs	Yes	RR 0.30 (0.19 to 0.49)	0
	1 RCT	No	One trial ineligible for pooling showed RR 0.65 (0.31 to 1.38)	NA
▪ TKR	1 RCT (1 comp)	No	RR 0.54 (0.25 to 1.16)	NA
▪ HFS	1 RCT	No	RR 0.06 (0.02 to 0.21)	NA
Distal DVT				
Prolonged prophylaxis versus standard duration prophylaxis	4 RCTs	Yes	RR 0.39 (0.15 to 1.04)	83.6
▪ 2001-present	2 RCTs	Yes	RR 0.33 (0.07 to 1.51)	NA
▪ THR	3 RCTs	Yes	RR 0.53 (0.24 to 1.17)	53.4
▪ TKR	1 RCT (1 comp)	No	RR 1.09 (0.67 to 1.78)	NA
▪ HFS	1 RCT	No	RR 0.02 (0.004 to 0.14)	NA
Major Bleeding				

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Prolonged prophylaxis versus standard duration prophylaxis	5 RCTs	Yes	OR 2.18 (0.73 to 6.51)	35.6
▪ 2001-present	3 RCTs	Yes	OR 2.76 (0.88 to 8.61)	22.3
▪ THR	2 RCTs	Yes	OR 0.98 (0.06 to 15.70)	NA
▪ TKR	1 RCT (1 comp)	No	OR 0.14 (0.003 to 6.95)	NA
▪ HFS	1 RCT	No	OR 3.40 (0.98 to 11.84)	NA
Major bleeding leading to reoperation				
Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 1.01 (0.14 to 7.18)	NA
Minor Bleeding				
Prolonged prophylaxis versus standard duration prophylaxis	3 RCTs	Yes	OR 2.44 (1.41 to 4.20)	0
▪ 2001-present	1 RCT	No	OR 2.39 (0.54 to 10.59)	NA
▪ THR	2 RCTs	Yes	OR 2.44 (1.36 to 4.39)	NA
▪ HFS	1 RCT	No	OR 2.39 (0.54 to 10.59)	---
Surgical site bleeding				
Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	OR 7.55 (1.51 to 37.64)	NA
Bleeding leading to infection				
Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Bleeding leading to transfusion				
Prolonged prophylaxis versus standard duration prophylaxis	2 RCTs	No	1 trial was excluded from the analysis because no events occurred in the groups compared; remaining trial showed RR 1.46 (0.85 to 2.51)	NA
▪ 2001-present	2 RCTs	No	1 trial was excluded from the analysis because no events occurred in the groups compared; remaining trial showed RR 1.46 (0.85 to 2.51)	NA
▪ THR	1 RCT	No	No events occurred in the groups compared	NA
▪ HFS	1 RCT	No	RR 1.46 (0.85 to 2.51)	NA
HIT				
Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	---
Discomfort				

Endpoint / Comparison	Type and Number of Studies	Pooled	Result	Statistical Heterogeneity I^2 (%)
Prolonged prophylaxis versus standard duration prophylaxis	0	---	---	--
Readmission				
Prolonged prophylaxis versus standard duration prophylaxis	1 RCT (2 comp)	Yes	RR 0.29 (0.96 to 1.34)	NA
▪ 2001-present	1 RCT (2 comp)	Yes	RR 0.29 (0.96 to 1.34)	NA
▪ THR	1 RCT (1 comp)	No	RR 0.13 (0.04 to 0.39)	NA
▪ TKR	1 RCT (1 comp)	No	RR 0.59 (0.24 to 1.44)	NA
Reoperation				
Prolonged prophylaxis versus standard duration prophylaxis	1 RCT	No	RR 0.21 (0.02 to 2.16)	NA

*: All base case analyses are represented in the table. Subgroup analyses without available data are not represented in this table. If only 1 trial was available subgroup analyses were not run.

Abbreviations: DVT=deep vein thrombosis; HFS=hip fracture surgery; HIT=heparin induced thrombocytopenia; LMWH=low molecular weight heparin; NA=Not Applicable; OR=Peto's Odds Ratio; PE=pulmonary embolism; PTS=post thrombotic syndrome; RCT=Randomized Controlled Trial; RR=Relative Risk; THR=total hip replacement; TKR=total knee replacement; UFH=unfractionated heparin; VKA=vitamin K antagonist

Key Question 9

In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter placement compared to any external mechanical intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, reoperation, and inferior vena cava filter placement associated insertion site thrombosis?

No randomized controlled trials or controlled observational studies met our inclusion criteria for this key question.

Key Question 10

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

Key Points

- There is a relative paucity of data comparing prophylactic strategies to no prophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery.
    - No randomized controlled trial or controlled observational studies evaluating elective spine surgery met inclusion criteria.
    - One trial evaluated the injectable low molecular weight heparin dalteparin versus placebo for 6 weeks in patients who had Achilles tendon rupture surgery. There were no significant differences in the occurrence of deep vein thrombosis or proximal deep vein thrombosis at 6 weeks. No patients presented with clinical pulmonary emboli or had episodes of major bleeding.

- One trial evaluated the injectable low molecular weight heparin dalteparin versus control for up to 30 days in patients who had arthroscopic knee surgery. Significantly fewer patients who received dalteparin developed a deep vein thrombosis or distal deep vein thrombosis. None of the deep vein thromboses were proximal. One patient in the dalteparin group developed a pulmonary embolism and also had a deep vein thrombosis. No patients had major bleeding and the occurrence of minor bleeding was not significantly different between the two groups.

Detailed Analysis

Study design and characteristics. Two randomized controlled trials (N=235) and no controlled observational studies evaluated the impact of prophylaxis versus no prophylaxis on final, intermediate, or adverse health outcomes. [181,182] The first trial by Lapidus and colleagues in 2007 enrolled patients who had Achilles tendon rupture surgery and randomized patients to receive the injectable low molecular weight heparin dalteparin versus placebo injections for 6 weeks.[182] This trial was published as a full text manuscript and was funded by industry and government/foundation. The mean age of enrolled patients ranged from 37 to 42 years and females represented 21 percent of the enrolled population. The mean weight ranged from 80 to 81 kilograms; obesity was not reported. None of the patients had a history of venous thromboembolsim and 5.8 to 11.3 percent of patients had the presence of varicosity. The history of malignancy or prior orthopedic surgery was not reported. The mean duration of surgery ranged from 44 to 45 minutes and 100 percent of participants received regional anesthesia. Tourniquet use was reported in 11.3 to 11.5 percent of patients. As this was an outpatient procedure patients were not hospitalized.

The second trial by Michot and colleagues in 2002 enrolled patients who had diagnostic or therapeutic arthroscopic knee surgery and were randomized to receive the injectable low molecular weight heparin dalteparin versus control for 30 days.[181] Diagnostic procedures were performed in 17 to 18 percent of patients while the majority of patients underwent therapeutic procedures (73 percent). Of the therapeutic procedures included, partial meniscectomy represented the majority of procedures (73.4 to 79.2 percent). The trial was published as a full text manuscript and the funding source was not disclosed. The mean age of enrolled patients ranged from 42.0 to 46.5 years and females represented 28.1 to 39.4 percent of the enrolled population. Mean body mass index was reported and ranged from 26.2 to 27.8 kilograms per meter squared. The presence of varicosity was reported in 12.1 to 14.1 percent of patients. The use of general anesthesia ranged from 29.7 to 33.3 percent, regional anesthesia ranged from 66.7 to 70.3 percent, and the use of both types of anesthesia ranged from 3.0 to 3.1 percent of the enrolled population. No other surgical characteristics were reported. As this was an outpatient procedure patients were not hospitalized.

Outcome evaluations.

Achilles tendon rupture surgery. One trial by Lapidus and colleagues enrolled 105 patients who had Achilles tendon rupture surgery and randomized patients to receive dalteparin 5000 units subcutaneously every day (n=52) or placebo saline injections daily (n=53) for six weeks.[182] After surgery, a below-knee plaster cast was applied in all patients and was replaced by another plaster cast or orthosis at three weeks at which time full weight bearing was allowed. Followup visits

were scheduled at three and six weeks at which time patients were screened clinically for signs and symptoms of deep vein thrombosis and pulmonary embolism and underwent unilateral color duplex sonography. Venography was used to confirm cases of deep vein thrombosis identified with sonography or when sonography was inconclusive.

In this trial, in patients who received dalteparin prophylaxis versus placebo, the risk of deep vein thrombosis (distal or proximal) was not significantly different at the sixth post-operative week (36.7 percent versus 40.4 percent, p = 0.80). The same result was seen when evaluating proximal deep vein thrombosis (2.0 percent versus 6.4 percent, p = 0.60). No patients presented with clinical signs or symptoms of pulmonary embolism during the followup period and no patients had major bleeding which was defined as bleeding requiring blood transfusion or into a critical organ (intraocular, intracranial, intraspinal or retroperitoneal).

Knee arthoscopy. One trial by Michot and colleagues enrolled 130 patients who had diagnostic or therapeutic arthroscopic knee surgery and randomized patients to receive dalteparin subcutaneous injections daily (n = 66) versus control (n = 64) up to 30 days post-operatively.[181] All patients received dalteparin 2500 units 60 to 120 minutes prior to the start of surgery and subsequent dosing was weight based; 2500 units daily if weighing less than or equal to 70 kilograms and 5000 units daily if weighting greater than 70 kilogram. Concomitant therapy with antiplatelet or anticoagulant therapy was not permitted. Patients were instructed to bear weight immediately after the surgery or as tolerated on crutches for 24 to 48 hours. Followup visits were scheduled on postoperative days 12 and 31 at which time patients were clinically examined for signs and symptoms of deep vein thrombosis, pulmonary embolism and adverse events. Bilateral compression ultrasonography was performed during these followup visits and venography was performed if ultrasonography was inconclusive. Patients were also instructed to report clinical signs earlier if they occurred, and physicians followed up by telephone every four days in patients who were randomized to daltaprin in between followup visits. Symptoms of deep vein thrombosis were confirmed with ultrasonography or venography and symptoms of pulmonary embolism were confirmed with ventilation-perfusion scans or angiography.

In this trial, the percent of patients with deep vein thrombosis was significantly decreased in those who received dalteparin prophylaxis versus control (1.5 percent versus 15.6 percent, p = 0.004). All deep vein thromboses were distal and occurred in the operated leg while none were proximal or in the contrlateral leg. Eight cases of deep vein thromboses were diagnosed at the first followup visit, 2 cases were diagnosed during the second followup visit, and 1 case was diagnosed on postoperative day 5 in the emergency room. Gender did not impact the effect of dalteparin versus placebo on the occurrence of deep vein thrombosis. One patient in the dalteparin group, who also had a distal deep vein thrombosis, developed a pulmonary embolism (1.5 percent) while none in the control group developed a pulmonary embolism (0 percent). No patients had major bleeding. There was no significant difference in the percent of patients who had minor bleeding in the dalteparin group versus control (12 percent versus 6 percent, p = 0.365).

Key Question 11

In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (injectable low molecular weight heparin versus unfractionated heparin versus factor Xa antagonists versus direct thrombin inhibitors) compared to mechanical interventions on

symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin induced thrombocytopenia, discomfort, readmission, and reoperation?

No randomized controlled trials or controlled observational studies met our inclusion criteria for this key question.

Strength of evidence and applicability

Strength of evidence. A summary of the strength of evidence for the base case analyses with a strength of evidence rating of low, moderate or high can be found in Table 4. The full strength of evidence evaluation for each outcome is presented in Appendix H.

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

Key question 2 evaluated the impact of patient, surgical or postsurgical characteristics on outcomes of interest. Overall data were insufficient for all patient characteristics with the exception of two; congestive heart failure and age. There was moderate strength of evidence that congestive heart failure increased the odds of symptomatic objectively confirmed venous thromboembolism and there was low strength of evidence that age did not impact the odds of symptomatic objectively confirmed venous thrombembolism and increased the odds of deep vein thrombosis, in major orthopedic surgery. Similarly, data were insufficient for all surgical or postsurgical characteristics with the exception of two comparisons; general versus regional anesthesia and cemented versus noncemented arthroplasty. There was low strength of evidence that patients who had general anesthesia had a higher risk of deep vein thrombosis compared to

regional anesthesia while there was no difference in the risk of proximal or distal deep vein thrombosis compared to regional anesthesia. There was also low strength of evidence that patients who had cemented arthroplasty had no difference in the risk of deep vein thrombosis or proximal deep vein thrombosis compared to noncemented arthroplasty.

In key question 3, there was insufficient evidence to determine the relationship between deep vein thrombosis and pulmonary embolism.

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

Key question 5 compared between pharmacologic and mechanical device classes. Compared with injectable unfractionated heparin, there was a high strength of evidence that low molecular weight heparin decreased the risk of proximal deep vein thrombosis and the odds of major bleeding although did not impact the risk of distal deep vein thrombosis. There was moderate strength of evidence that low molecular weight heparin agents decreased the odds of pulmonary embolism, heparin induced thrombocytopenia and the risk of deep vein thrombosis, although did not impact the risk of mortality or minor bleeding. There was low strength of evidence that there was no difference in the risk of nonfatal pulmonary embolism, asymptomatic or symptomatic deep vein thrombosis, surgical site bleeding or readmission. Compared with factor Xa antagonists, there was high strength of evidence the low molecular weight heparins increased the risk of deep vein thrombosis and distal deep vein thrombosis and moderate evidence low molecular weight heparins increased the odds of proximal deep vein thrombosis while decreasing the odds of major bleeding. There was moderate strength of evidence that there was no difference in the odds of nonfatal pulmonary embolism, mortality, symptomatic deep vein thrombosis, or major bleeding leading to reoperation. There was low strength of evidence that there was no difference in the odds of symptomatic objectively confirmed venous thromboembolism or fatal pulmonary embolism. Compared with vitamin K antagonists, there was high strength of evidence that low molecular weight heparins increased the odds of major bleeding and moderate strength of evidence they increased the odds of minor bleeding and low strength of evidence they increased the odds of surgical site bleeding. Strength of evidence was moderate that low molecular weight heparins decreased the risk of proximal deep vein thrombosis and low that they decreased the risk of deep vein thrombosis. Strength of evidence was moderate that there was no difference in the odds of pulmonary embolism, mortality and symptomatic deep vein thrombosis and low that there was no difference in the risk of proximal deep vein thrombosis or the odds of symptomatic objectively confirmed venous thromboembolism or nonfatal pulmonary embolism. All other outcomes were rated as insufficient.

For both the comparisons of low molecular weight heparin with direct thrombin inhibitors and with mechanical prophylaxis, there were no significant differences between the two classes. Compared with injectable or oral direct thrombin inhibitors, there was high strength of evidence

that there was no difference with the use of injectable low molecular weight heparin agents in the risk of bleeding leading to transfusion and there was moderate strength of evidence that there was no difference in the risk of major venous thromboembolism, pulmonary embolism, mortality, asymptomatic or symptomatic deep vein thrombosis, major bleeding, major bleeding leading to reoperation or minor bleeding. The strength of evidence was low that there was no difference in the odds of fatal or nonfatal pulmonary embolism or the risk of proximal deep vein thrombosis. Other outcomes were rated as insufficient. For the comparison of injectable low molecular weight heparin to mechanical prophylaxis, few studies were available and most outcomes were rated as insufficient. There was moderate strength of evidence that there was no significant difference in the risk of deep vein thrombosis, proximal or distal deep vein thrombosis and there was moderate strength of evidence that there was no difference in the odds of mortality and readmission.

For other class comparisons, there was relatively less data and more outcomes were rated with insufficient evidence. Compared with oral or injectable direct thrombin inhibitors, there was moderate strength of evidence that injectable unfractionated heparin increased the risk of deep vein thrombosis and the odds of proximal deep vein thrombosis while there was low strength of evidence that there was no difference in the risk of pulmonary embolism, fatal pulmonary embolism, mortality, or major bleeding leading to reoperation. Compared to mechanical prophylaxis, there was moderate strength of evidence that oral vitamin K antagonists decreased the risk of proximal deep vein thrombosis with a low strength of evidence that there was no difference in the risk of deep vein thrombosis or minor bleeding. Compared with mechanical prophylaxis there was moderate strength of evidence that oral antiplatelet prophylaxis increased the risk of deep vein thrombosis. All other outcomes were rated as insufficient for this comparison. All outcomes were rated as insufficient for the following comparisons: oral anitplatelet versus oral vitamin K antagonists, injectable unfractionated heparin versus factor Xa antagonists, and injectable unfractionated heparin versus mechanical prophylaxis.

Key question 6 compared agents within the low molecular weight heparin class as well as within mechanical devices. Overall there were very few comparative studies and those evaluated had very low event rates. Therefore the majority of outcomes were rated with insufficient strength of evidence. There was insufficient evidence for all outcomes when comparing specific mechanical devices, as although two studies compared specific mechanical devices, they each compared different devices. When compared to graduated compression devices, intermittent pneumatic compression devices decreased the risk of overall and distal deep vein thrombosis, while there was no difference in the risk of proximal deep vein thrombosis, each with a low strength of evidence. When comparing enoxaparin to other low molecular weight heparins (dalteparin or tinzaparin), there was no difference in the risk of overall or proximal deep vein thrombosis, or in the odds of surgical site bleeding, all with low strength of evidence. There was moderate strength of evidence that there as no difference in the risk of major bleeding, while all other outcomes were rated insufficient.

Very few trials compared combination pharmacologic and mechanical prophylaxis versus one of the methods alone, and therefore the majority of outcomes were rated with insufficient strength of evidence in key question 7. When comparing pharmacologic plus mechanical to pharmacologic prophylaxis alone, there was moderate strength of evidence that combination therapy decreased the risk of deep vein thrombosis and had no difference on the risk of distal deep vein thrombosis compared to single modality. There was low strength of evidence that there was no difference in the odds of pulmonary embolism, nonfatal pulmonary embolism, or

proximal deep vein thrombosis. When comparing pharmacologic plus mechanical versus mechanical prophylaxis, there was low strength of evidence that there was no difference in the risk of proximal deep vein thrombosis. All other outcomes for both comparisons were rated insufficient.

Relative to other key questions evaluating prophylaxis in major orthopedic surgery, key question 8 had the highest overall strength of evidence for outcomes evaluated. Overall there is a better comparative balance of benefits to harms for prolonging prophylaxis. There was high strength of evidence that prolonged prophylaxis decreased the risk of pulmonary embolism, asymptomatic or symptomatic or proximal deep vein thrombosis, moderate strength of evidence that prolonged prophylaxis decreased the risk of symptomatic objectively confirmed venous thromboembolism, deep vein thrombosis, and the odds of nonfatal pulmonary embolism. There was low strength of evidence that there was no difference in the risk of distal deep vein thrombosis, readmission or odds of major bleeding. The one harm which had high strength of evidence was the risk of minor bleeding, which was increased with prolonged prophylaxis. Other outcomes were rated as insufficient.

No trials or studies met inclusion criteria for key question 9 therefore all outcomes were rated insufficient.

In other orthopedic surgeries evaluated in this report, there were two trials which met inclusion criteria for key question 10; one trial in knee arthroscopy, one trial in Achilles tendon rupture repair, and no trials in elective spine surgery. Therefore the overall strength of evidence was insufficient for all outcomes evaluated in these patient populations. No trials met inclusion criteria for key question 11 therefore all outcomes were rated insufficient.

Applicability of the body of evidence. A summary of the applicability of the evidence for the base case analyses with a strength of evidence rating of low, moderate or high can be found in Table 4. The full rating of the applicability of the body of evidence and the applicability of each included trial and study are presented in Appendix I.

For key question 1, the overall applicability was low for all outcomes with exception of major bleeding, minor bleeding and bleeding leading to transfusion in total hip replacement surgery which had moderate applicability. Although each major orthopedic surgery was considered separately when estimating the incidence of outcomes, the majority of trials and in many cases the only trials available were conducted outside of the United States. Surgical and post surgical characteristics, training, and expertise in other countries may not reflect that within the United States. Additionally, some trials were conducted in the 1980's as opposed to the 1990's or within the 2000's, which may be subject changes in surgical techniques and patient care over time.

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

Key question 3 had moderate applicability as most of the data was derived from trials and studies conducted in the United States and within the 1990's although one limitation is the majority of data were in knee replacement surgery with little from hip fracture surgery.

For key questions 4 through 8, similar criteria were common reasons for scoring a comparison and outcome lower for applicability. Overall applicability was often limited because one or two of the major orthopedic surgeries were not evaluated, duration of followup was inadequate to evaluate the given outcome, and many trials were conducted outside of the United States and sometimes represented a majority of the available data. Specifically for key question 6, the specificity of the comparisons within the given studies applicability was rated low for the great majority of outcomes and comparisons. Data were often highly applicable to a specific device comparison within one or two of the major orthopedic surgeries. Hip fracture surgery was general not evaluated. In comparison of low molecular weight heparins, the majority of trials were conducted outside of the United States and for a given outcome, usually either tinzaparin or dalteparin were compared to enoxaparin (not both) in one major orthopedic surgery. Specific to key question 7, due to the paucity of available literature, conclusions were sometimes based on a specific combination compared to a single modality in one of the major orthopedic surgeries and therefore the overall applicability of the evidence to combination versus single modality in major orthopedic surgery is limited. In comparing combination prophylaxis to mechanical prophylaxis alone, most comparisons were only in hip replacement surgery. Specific to key question 8, the main limitation to the overall applicability was the lack of variety of pharmacologic classes evaluated. Almost all trials compared shorter versus longer term use of low molecular weight heparins and therefore, the applicability to other classes is limited. Often the majority of trials were conducted outside of the United States.

Discussion

A summary of the results with a strength of evidence rating of low, moderate, or high for Key Questions 1 through 8 of our CER can be found in Table 4. Evaluations for Key Questions 9 through 11 had insufficient strength of evidence and are not included. To see how our strength and applicability of evidence ratings were derived, please see Appendicies H and I. For more detailed analysis of our results or to see results for comparisons with an insufficient strength of evidence rating, please see the results section for that key question. Although major orthopedic surgery is inclusive of total hip or knee replacement surgery and hip fracture surgery, the vast majority of literature evaluated hip or knee replacement surgery with very little evaluation of hip fracture surgery. No literature was found evaluating health related quality of life or post thrombotic syndrome as outcomes while harms such as bleeding leading to infection, bleeding leading to transfusion, readmission, and reoperation were rarely reported. No trials or studies were found to evaluate the comparative effectiveness of inferior vena cava filters with mechanical prophylaxis in major orthopedic surgery where as comparative data of prophylaxis to no prophylaxis or between injectable and mechanical prophylaxis in other nonmajor orthopedic surgeries was very limited.

Where applicable, we compare our results to those derived from previous meta-analyses as typified in Table 5 and Table 6. We used more recent search dates and generally used more restrictive inclusion and exclusion criteria than other meta-analyses including more stringent criteria for diagnosing deep venous thrombosis and pulmonary embolism endpoints. We also limited our evaluation to medications or mechanical devices available for use within the United States.

In key question 1 we limited our inclusion criteria to placebo or control arms of trials for pulmonary embolism and deep vein thrombosis outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native incidence of deep vein thrombosis events is still relatively high but pulmonary embolism and bleeding events are rarer. In total hip replacement, total knee replacement, and hip fracture surgery, respectively, the incidence of deep vein thrombosis (39 percent, 53 percent, 47 percent), proximal deep vein thrombosis (32 percent, 17 percent, --), distal deep vein thrombosis (30 percent, 30 percent, --), pulmonary embolism (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (6 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --) are reported in clinical trials. There was high heterogeneity which could reflect different time periods of followup, different definitions of events, and different ethnicities and countries in trials. Our results are similar to that of previous pooled-analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001 where 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding as shown in Table 5.[144,150,155,160,162] Using our stringent inclusion and exclusion criteria, including more stringent definitions of outcomes, and allowing trials and studies right up to the present day are strengths of our comparative effectiveness review.

In key question 2, several randomized controlled trials identified through our literature search evaluated different surgical characteristics on outcomes of interest including anesthetic regimen, cemented arthroplasty, tourniquet use, limb positioning, and fibrin adhesive use. However, few trials evaluated each characteristic and subsequently did not address all major orthopedic

procedures. Additionally, most trials evaluated intermediate health outcomes and did not address final health outcomes and only one trial evaluated bleeding outcomes. As such, pooling was not possible. The surgical comparison with the most identified data was general anesthesia versus regional anesthesia. The impact of general versus regional anesthesia on several measures of deep vein thrombosis (overall, asymptomatic, proximal) was favorable to neutral for regional anesthesia while distal and symptomatic deep vein thrombosis, pulmonary embolism, and major bleeding were neutral. In a previous meta-analysis of 21 studies, regional anesthesia was associated with a nonsignificantly reduced odds of pulmonary embolism and a significantly reduced odds of deep vein thrombosis with no real impact on mortality versus general anesthesia.[153] We did not pool the results from our six included trials because many of the trials did not maintain similar prophylaxis regimens between groups or between genders reducing our confidence in the similarity between the groups.

Although one trial compared spinal versus epidural anesthesia on the risk of deep vein thrombosis, no events occurred in the groups compared. The other surgical characteristics were too limited to make any determinations.

Patient characteristics were primarily evaluated in multivariate regression analyses of observational studies. Few characteristics were evaluated in multiple studies and often times when a significant finding was observed, the magnitude or direction of the effect was not reported. There was no data regarding harms. Patient characteristics that were found to significantly increase the odds of symptomatic objectively confirmed venous thromboembolism in all available studies included congestive heart failure (two studies), inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric fracture (one study), subtrochanteric fracture (one study), increased hemoglobin (one study), personal or familial history of venous thromboembolism, (one study), and varicose veins (one study). Patient characteristics consistently found to increase the odds of pulmonary embolism (evaluated in one study each) included age and genitourinary infection while cardiovascular disease was found to decrease the odds of pulmonary embolism. The following characteristics showed a mixed effect on deep vein thrombosis: age (two studies showed a significant increase while one study showed no effect), obesity (one study showed a significant increase while one study showed no effect), and gender (one study showed a significant increase in females while one study showed gender had no effect). Metabolic syndrome increased the odds of symptomatic deep vein thrombosis while congestive heart failure increased the odds of proximal deep vein thrombosis in the single study that evaluated each covariate.

In key question 3, no trials or studies were available assessing whether DVT was correlated with, or a multivariate predictor of, PE. This data may be limited because the routine use of prophylaxis may have reduced the occurrence of deep vein thrombosis and the scheduled anticoagulant treatment for deep vein thrombosis once it was detected may have diminished the percentage that developed into pulmonary embolism. In one observational study in total knee replacement surgery, the overall occurrence of pulmonary embolism and the subset with symptomatic pulmonary embolism occurred more frequently in those with deep vein thrombosis. However the data was not adjusted for confounders and we cannot discern whether these variables are correlated or colinear.

In key question 4, the comparative balance of benefits to harms for providing pharmacologic prophylaxis versus no prophylaxis is favorable. There is moderate evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases deep vein thrombosis (overall, proximal, and distal) in patients undergoing major orthopedic surgery. There is low evidence that

pharmacologic prophylaxis versus no prophylaxis significantly decreases major venous thromboembolism and asymptomatic deep vein thrombosis in patients undergoing major orthopedic surgery. Pharmacologic prophylaxis did not significantly impact pulmonary embolism in the base case analysis, although it was trending in that direction, and significantly reduced the risk of pulmonary embolism in the most stringent trials where they did not allow any background prophylaxis (such as compressions stockings) in the experimental groups. There is moderate evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis does not significantly impact nonfatal pulmonary embolism, mortality, symptomatic deep vein thrombosis or major bleeding in patients undergoing major orthopedic surgery. We cannot determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group. Our results are in general agreement with the six previous meta-analyses of trials comparing pharmacologic prophylaxis versus placebo/control in patients with major orthopedic surgery (Table 6).[151,152,159,170,175,179] Four assessed low molecular weight heparin versus placebo/control, one evaluated low molecular weight heparin or unfractionated heparin versus placebo/control, and the last compared vitamin K antagonists versus placebo. In the most recent meta-analysis comparing low molecular weight heparins versus placebo, there was a significant reduction in the odds of nonfatal pulmonary embolism with nonsignificant reductions in mortality and major bleeding. Deep vein thrombosis was not assessed in this meta-analysis but in the previous three meta-analyses was found to be significantly reduced with low molecular weight heparin use versus placebo/control. When either low molecular weight heparins or unfractionated heparin was compared to placebo/control deep vein thrombosis (overall, proximal, and deep) were significantly reduced but no significant impact on pulmonary embolism was found or death was found. In another meta-analysis, vitamin K antagonists significantly reduced pulmonary embolism and deep vein thrombosis but nonsignificantly increased major bleeding versus placebo.

The comparative balance of benefits to harms for providing mechanical prophylaxis versus no prophylaxis is possibly favorable but more data is needed to support this assumption. There is a low level of evidence that mechanical prophylaxis versus no prophylaxis significantly decreases the occurrence of deep vein thrombosis in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal deep vein thrombosis in patients undergoing major orthopedic surgery, the power to detect these differences is low. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use so benefits would likely overwhelm the risk of harms. In the only meta-analysis comparing mechanical prophylaxis (intermittent pneumatic compression and venous foot pump) versus control, the risk of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduce (Table 6).[151]

In key question 5, we sought to determine the impact of therapy on numerous outcomes but were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, there was either a lack of evaluable data or no significant differences. We cannot determine if this means that there is a lack of effect versus a lack of power to show that it is significant.

Low molecular weight heparin agents, as a class, have a better comparative balance of benefits to harms versus unfractionated heparin with significantly fewer pulmonary embolisms, deep vein thromboses, proximal deep vein thromboses, major bleeding, and heparin induced thrombocytopenia events. The comparative balance of benefits to harms for low molecular weight heparins to other classes cannot be readily determined. Low molecular weight heparin agents are also superior to vitamin K antagonists at reducing measures of deep vein thromboses (any, asymptomatic, proximal, and distal) but increase major, minor, and surgical site bleeding. Since no significant differences were found in important final health outcomes, the relevance of these reductions in deep vein thrombosis needs to be considered. Low molecular weight heparin agents may be inferior to factor Xa antagonists in terms of any, proximal, and distal deep vein thromboses but have a lower risk of major and minor bleeding. Observational data suggested low molecular weight heparin agents had decreased mortality although this was not supported by data pooled from randomized trials which showed no significant difference. The comparison of low molecular weight heparins agents to direct thrombin inhibitors is difficult because the occurrence of deep vein thrombosis is greater but the occurrence of distal deep vein thrombosis is less with low molecular weight heparin agents and while surgical site bleeding is higher with low molecular weight heparin therapy, the overall risk of serious bleeding was not significantly altered. Finally, when low molecular weight heparin agents are compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving low molecular weight heparin agents. The results of previous meta-analyses are in general agreement with the findings of our comparative effectiveness review. In six previous meta-analyses, low molecular weight heparins were compared to unfractionated heparin in patients with major orthopedic surgery (Table 6) [143,151,152,161,178,179] There were significant reductions in deep vein thrombosis (five of six meta-analyses), proximal deep vein thromboses (two of three meta-analyses with the third showing a nonsignificant reduction), and major bleeding (one of three meta-analyses with a nonsignificant reductions in the second and third) with low molecular weight heparins versus unfractionated heparin. There was a nonsignificant reduction in mortality (two of two meta-analyses), mixed effects on pulmonary embolism (one meta-analysis showing a significant reduction, one showing a nonsignificant increase the other showing a nonsignificant decrease), and a nonsignificant increase in any bleeding with low molecular weight heparins versus unfractionated heparin. In two previous meta-analyses, the impact of dabigatran versus enoxaparin in total hip and total knee arthroplasty outcomes was assessed.[173,176] No significant differences in venous thromboembolism or major bleeding were seen. Four meta-analyses comparing vitamin K antagonists to low molecular weight heparins.[152,159,161,172] The three meta-analyses evaluating deep vein thrombosis found a significant increase while the one of two meta-analyses evaluating major bleeding found a significant decrease and another found a nonsignificant decrease with vitamin K antagonist use versus low molecular weight heparins. One meta-analysis found a nonsignificant increase in pulmonary embolism and death while another found a nonsignificant increase in symptomatic pulmonary embolism. One meta-analysis compared the factor Xa inhibitor fondaparinux to the low molecular weight heparin enoxaparin and the odds of venous thromboembolism and proximal deep vein thrombosis was significantly reduced.

It is difficult to discern the comparative balance of benefits to harms for oral antiplatelet therapy versus mechanical prophylaxis or vitamin K antagonists. Oral antiplatelet therapy had significantly greater occurrence of any and distal deep vein thrombosis versus mechanical prophylaxis. In a controlled observational study, oral vitamin K antagonists had significantly

fewer fatal pulmonary embolism events versus oral antiplatelet agents. In the only available randomized trial comparing vitamin K antagonists to oral antiplatelet agents, the same direction of effect was found suggesting vitamin K antagonist superiority but this was not significant. Mortality was higher in patients receiving aspirin versus warfarin in one observational study, was nonsignificantly trending in that direction in another observational study but showed no difference in a clinical trial. These results are characteristically similar to a previous meta-analysis which found that vitamin K antagonists nonsignificantly decreased overall deep vein thrombosis but nonsignificantly increased proximal deep vein thrombosis with no real difference in major hemorrhage (Table 6).[159]

Unfractionated heparin, which was found to be inferior to low molecular weight heparin agents in the balance of benefits to harms, had a greater occurrence of death and major bleeding versus factor Xa antagonists in an observational study (with no clinical trial data to support or refute the findings), had a greater occurrence of any and proximal deep vein thrombosis versus direct thrombin inhibitors, and had a greater occurrence of deep vein thrombosis versus mechanical prophylaxis. As such, it is likely inferior to factor Xa inhibitors in the balance of benefits to harms as well.

Patients receiving vitamin K antagonists had less occurrence of proximal deep vein thrombosis versus mechanical prophylaxis but with no other differences in other health outcomes or bleeding, it is hard to discern a difference in the balance of efficacy to harms between them. This is consistent with a previous meta-analysis that found nonsignificant decrease in proximal deep vein thrombosis but nonsignificant increases in mortality, asymptomatic deep vein thrombosis, and major hemorrhage (Table 6).[159]

In key question 6, there were no significant differences in pulmonary embolism (any, fatal, and nonfatal), mortality, and mortality due to bleeding between modalities within low molecular weight heparin and mechanical device classes but these evaluations were based on one or two trials with either no events or a very low number of events.

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

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

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

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

In key question 7, the balance of benefits to harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic surgery cannot be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis does not significantly impact nonfatal pulmonary embolism, mortality, or deep vein thrombosis subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There is moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of deep vein thrombosis versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes cannot be determined.

For key question 8, the balance of benefits to harms for prolonged versus shorter term prophylaxis in patients undergoing major orthopedic surgery is favorable. The impact of prolonging prophylaxis for 28 days or longer on events was compared to prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. In base case analyses, prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed venous thromboembolism, pulmonary embolism (overall and nonfatal), and deep vein thrombosis (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. While higher heterogeneity was found for symptomatic venous thromboembolism and deep vein thrombosis, the direction of effect was consistent between all of the trials. In base case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis. Four previous meta-analyses compared the impact of longer versus shorter duration pharmacologic prophylaxis and are in general agreement with our present comparative effectiveness review (Table 6). [147,154,165,177] Decreases in deep venous thrombosis (overall, symptomatic, asymptomatic, and proximal) and venous thromboembolism were found with nonsignificant increases on minor bleeding but not major bleeding in these meta-analyses.

For key questions 9 and 11, there were no trials or studies that met our inclusion criteria. For key question 10, one trial was available for Achilles tendon rupture and for knee arthroscopy but no literature met inclusion criteria for elective spine surgery. Both of the available trials were small in size leading to limited power to detect differences between the groups compared. The comparative balance of benefits to harms for dalteparin therapy versus placebo or control is difficult to discern based on the scant data. In patients who had surgical repair of Achilles tendon rupture, the use of dalteparin versus placebo for six weeks did not significantly impact the incidence of total or proximal deep vein thrombosis. No patients developed a pulmonary embolism or major bleeding. In patients who had arthroscopic knee surgery, the use of dalteparin versus control led to significantly fewer patients with total or distal deep vein thrombosis. One patient in the dalteparin group developed a pulmonary embolism and also had a deep vein thrombosis. No patients had major bleeding and the occurrence of minor bleeding was not significantly different between the two groups.

Future Research

Limitations of current research

- In total hip replacement, total knee replacement, and hip fracture surgery there are numerous limitations to the current literature base that need to be appreciated.
    - While we found that there is a real risk of developing deep vein thrombosis, pulmonary embolism, and major bleeding after undergoing major orthopedic surgery, there is inadequate data to say whether or not deep vein thrombosis causes pulmonary embolism. We were not even able to determine that deep vein thrombosis is an independent predictor of pulmonary embolism. With prophylaxis to prevent deep vein thrombosis and pulmonary embolism and the use of active treatment of deep vein thrombosis to prevent pulmonary embolism, it is difficult to assess this linkage. In addition, we had no data to assess the linkage between deep vein thrombosis and other final health outcomes. This creates a dilemma for patients, healthcare decision makers, and clinicians when the endpoint most commonly evaluated in the prophylaxis trials is deep vein thrombosis.
    - Other than showing the superiority in the balance of benefits to harms for low molecular weight heparins versus unfractionated heparin, whether one class is superior to another class cannot be clearly determined. In a few cases, there are offsetting benefit and harms effects and in many cases, there just is not ample evidence to assess. While it seems that low molecular weight heparins enoxaparin, dalteparin, tinzaparin) have similar effects, we cannot determine if an agent within any other class is superior to another agent within the same class.
    - The large variety and number of mechanical devices makes it hard to know how data can be extrapolated from one device to others in the same or different classes. Mechanical device trials are by and large devoid of harms evaluations.
    - We cannot discern the comparative benefits and harms of using both pharmacologic and mechanical prophylaxis versus either modality alone.
    - Further research is needed to determine independent predictors of intermediate, final health, and harms outcomes. Current literature is too scant to reliably determine the impact of surgical or patient characteristics on these outcomes.
    - We could not determine the comparative benefits and harms of using inferior vena cava filters with mechanical prophylaxis in major orthopedic surgery as no literature met our inclusion criteria.
- When we assess orthopedic surgeries other than total hip replacement, total knee replacement or hip fracture surgery, we do not have an adequate literature base to determine benefits or harms.

Future research avenues

- In total hip replacement, total knee replacement, and hip fracture surgery there are several avenues for future research:
    - Since the linkage between deep vein thrombosis and venous thromboembolism, pulmonary embolism, postthrombotic syndrome, or mortality has not been shown, future comparative trials should focus on these final health outcomes or should explicitly show the linkage between deep vein thrombosis and these final health

outcomes. It would not be sufficient just to show a correction between these outcomes.
    - Future trials evaluating prophylaxis within major orthopedic surgery should include more outcomes assessing harms such as bleeding leading to infection, bleeding leading to transfusion, readmission and reoperation to provide more information for the comparative balance of benefits to harms. Additionally patient important outcomes such as health related quality of life and post thrombotic syndrome should be included.
    - Future observational studies should be designed to determine if there are surgical or patient factors that predict the occurrence of these outcomes. We have identified several promising predictors but need future evaluations to help determine their importance.
        - For regional versus general surgery, an adequately powered randomized controlled trial is needed to determine if anesthesia type impacts patient outcomes.
    - Future within class and between class comparative trials are needed. In several classes, both oral and intravenous methods of pharmacologic prophylaxis will be available and should be directly evaluated. More attention to assessing for final health outcomes and harms will be needed in these trials. Especially given the benefits of prolonged prophylaxis versus short term prophylaxis, the impact of oral therapy on patient perceived quality of life will be an important endpoint to consider. If a greater number of between class trials are conducted, mixed treatment comparison meta-analyses could be conducted to assess for indirect comparisons but presently, the literature base seems too sparse to conduct such an analysis.
    - Future trials comparing the benefits and harms of using both dual modality versus single modality prophylaxis alone are needed.
    - Further research is needed to determine independent predictors of intermediate, final health, and harms outcomes. Current literature is too scant to reliably determine the impact of surgical or patient characteristics on these outcomes
    - Future trials comparing the benefits and harms of using inferior vena cava filters versus mechanical prophylaxis are needed.
- Future trials in nonmajor orthopedic surgeries should determine whether or not prophylaxis is superior to control and the comparative effectiveness of different prophylactic options.

List of acronyms/abbreviations

Acronym/Abbreviation	Definition
AOR	Adjusted odds ratio
CI	Confidence interval
EPC	Evidence-based Practice Center
Mg	milligrams
NNH	Number needed to harm
NNT	Number needed to treat
OR	Peto's odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative risk

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