Comparative Effectiveness Review
Number 49

Effective Health Care Program

Venous Thromboembolism Prophylaxis in Orthopedic Surgery

Executive Summary

Background

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

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

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superior to single modality therapy, and the comparative effectiveness of different pharmacologic or mechanical modalities have not been adequately systematically reviewed. Lastly, in contemporary practice, the risks of VTE, PE, and DVT and the causal link between DVT and PE have not been well established.[2]

Objectives

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

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

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

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

KQ 4: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, post thrombotic syndrome (PTS), mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia (HIT), discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins [LMWHs], injectable unfractionated heparin [UFH], injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors [DTIs], oral vitamin K antagonists [VKAs]) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump).

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

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

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

KQ 8: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or

longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?

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

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

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

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

Methods

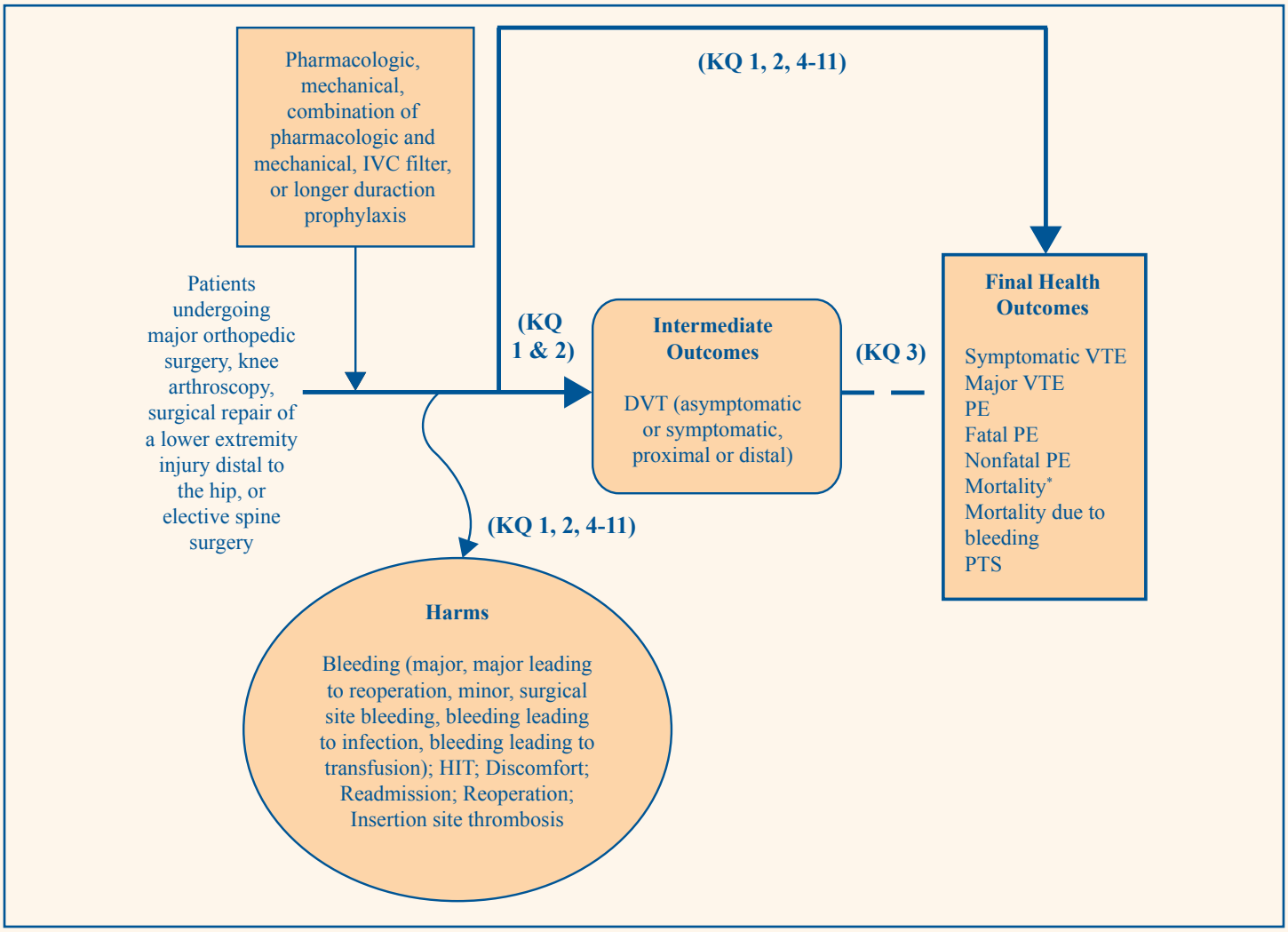
Input From Stakeholders

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

Data Sources and Selection

A systematic literature search of Medline, the Cochrane Central Register of Controlled Trials, and Scopus from 1980 to September 2010 was conducted with no language restrictions. The year 1980 was used as a restriction to reflect contemporary practice. Two separate literature searches were conducted. The first search was used to identify studies that evaluated pharmacologic, mechanical, or inferior vena cava filter methods of thromboprophylaxis in patients undergoing major orthopedic surgery, describe the association between patient, surgical, or postsurgical characteristics and VTE or bleeding, or describe the association between intermediate and final health outcomes to answer KQs 1 through 9. The second search was used to identify studies which evaluate pharmacologic or

Figure A. Analytic Framework



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

*Mortality is all-cause mortality.

mechanical methods of thromboprophylaxis in patients undergoing knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery to answer KQs 10 and 11. Backward citation tracking was also conducted. A grey literature search of regulatory documents, abstracts, and ongoing clinical trials was conducted by the Scientific Resource Center and reviewed by two independent investigators for inclusion into our literature base by applying the same a priori defined inclusion criteria defined below. The literature searches were updated in May 2011.

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

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

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

Data Extraction and Quality Assessment

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

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

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

Data Synthesis and Analysis

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

publication bias. Statistics were performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England).

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

Results

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

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

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

KQ 1: Data were limited to placebo or control arms of trials for PE and DVT outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native postoperative incidence of DVT events was highest followed by PE and bleeding events. Followup periods were defined in most trials as the postoperative period and may imply a more immediate rather than longer term followup. The strength of evidence is predominately low for outcomes evaluated in hip and knee replacement surgery while all outcomes in hip fracture surgery were rated with insufficient evidence. Not all three surgeries had incidence data reported in clinical trials; therefore, the symbol "--" is used when no data were reported for the given surgery and outcome. In THR, TKR, and HFS, respectively, the incidences were: DVT (39 percent, 46 percent, 47 percent), proximal DVT (32 percent, 17 percent, --), distal DVT (30 percent, 22 percent, --), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (5 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --). Statistically significant levels of publication bias were detected for major bleeding and minor bleeding in THR, suggesting an underestimation of the incidence, which directionality of publication bias for proximal DVT in THR was unclear. Although RCTs and studies that used objective diagnostic means to confirm efficacy outcomes were included as opposed to less rigorous criteria, a high degree of heterogeneity was present for most outcomes. This may be due to additional factors, such as different definitions of events, different ethnicities and countries in which trials were conducted, and undefined periods of postoperative followup and variation in duration of followup, potentially leading to insufficient length of followup for the outcomes being assessed. Our results are similar to that of previous pooled analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001, in which 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding.

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

compared. The other characteristics were too limited to make any determinations.

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

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

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

Providing mechanical prophylaxis versus no prophylaxis may have a better comparative balance of benefits and harms, but more data are needed to support this assumption. One RCT found that mechanical prophylaxis versus no prophylaxis significantly decreased the occurrence of DVT in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal DVT in patients undergoing major orthopedic surgery, the power to detect these differences was low. In the only previous meta-analysis comparing mechanical prophylaxis (intermittent pneumatic

compression and venous foot pump) versus control, the risks of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduced. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use, so benefits would likely overwhelm the risk of harms.

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

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

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

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

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

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

The balance of benefits and harms from using enoxaparin versus another low molecular weight heparin within the class (dalteparin or tinzaparin) is similar. No difference in the occurrence of DVT or proximal DVT occurred between LMWHs (enoxaparin versus either tinzaparin or dalteparin). No significant difference was seen in

asymptomatic DVT between enoxaparin and dalteparin, symptomatic DVT between enoxaparin and tinzaparin, or distal DVT between enoxaparin and tinzaparin. For major bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. For surgical site bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For HIT, one trial found no significant difference between enoxaparin and tinzaparin for this outcome.

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

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

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

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

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

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

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

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

Figure B. PRISMA flow diagram for search one

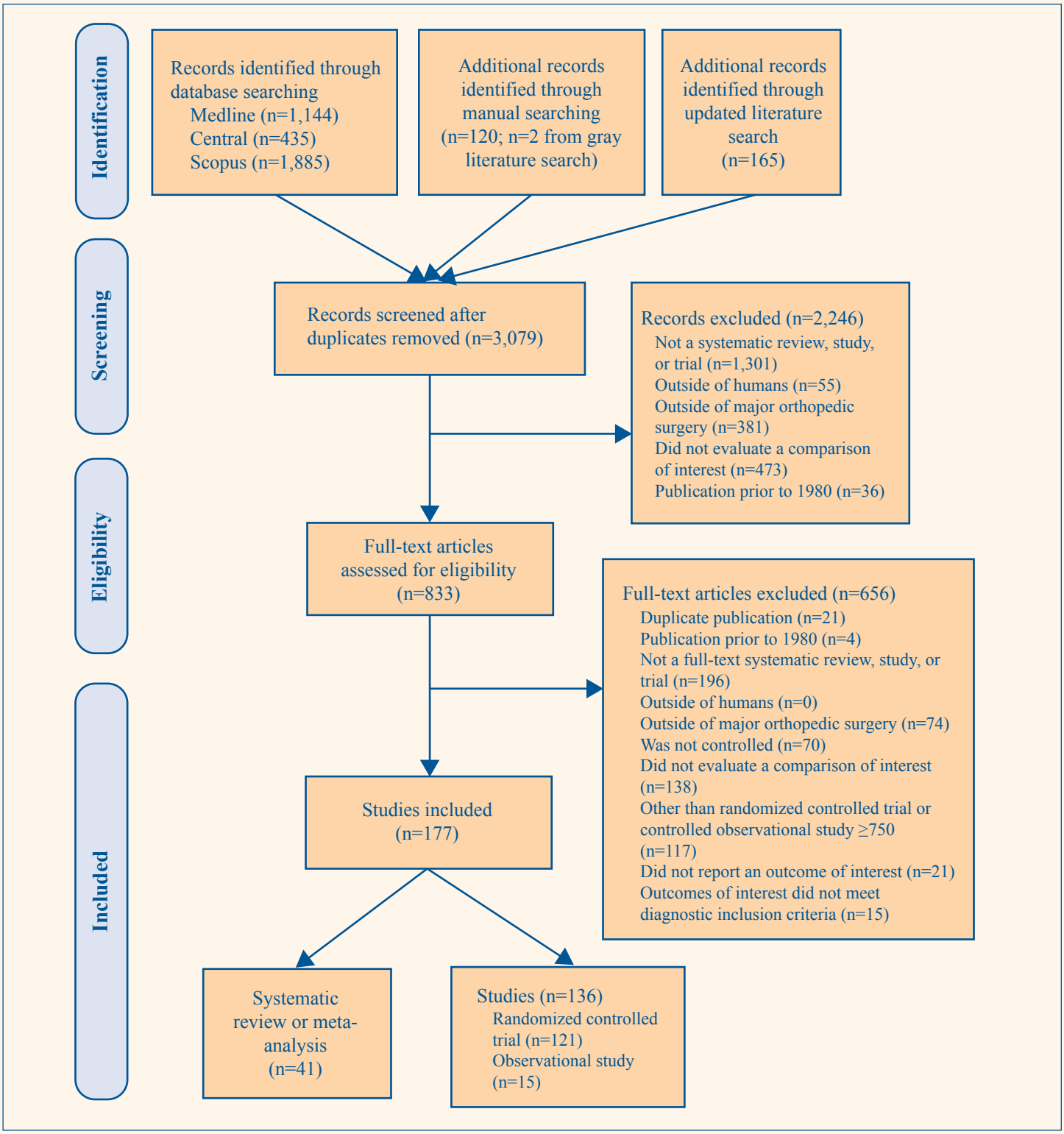


Figure C. PRISMA flow diagram for search two

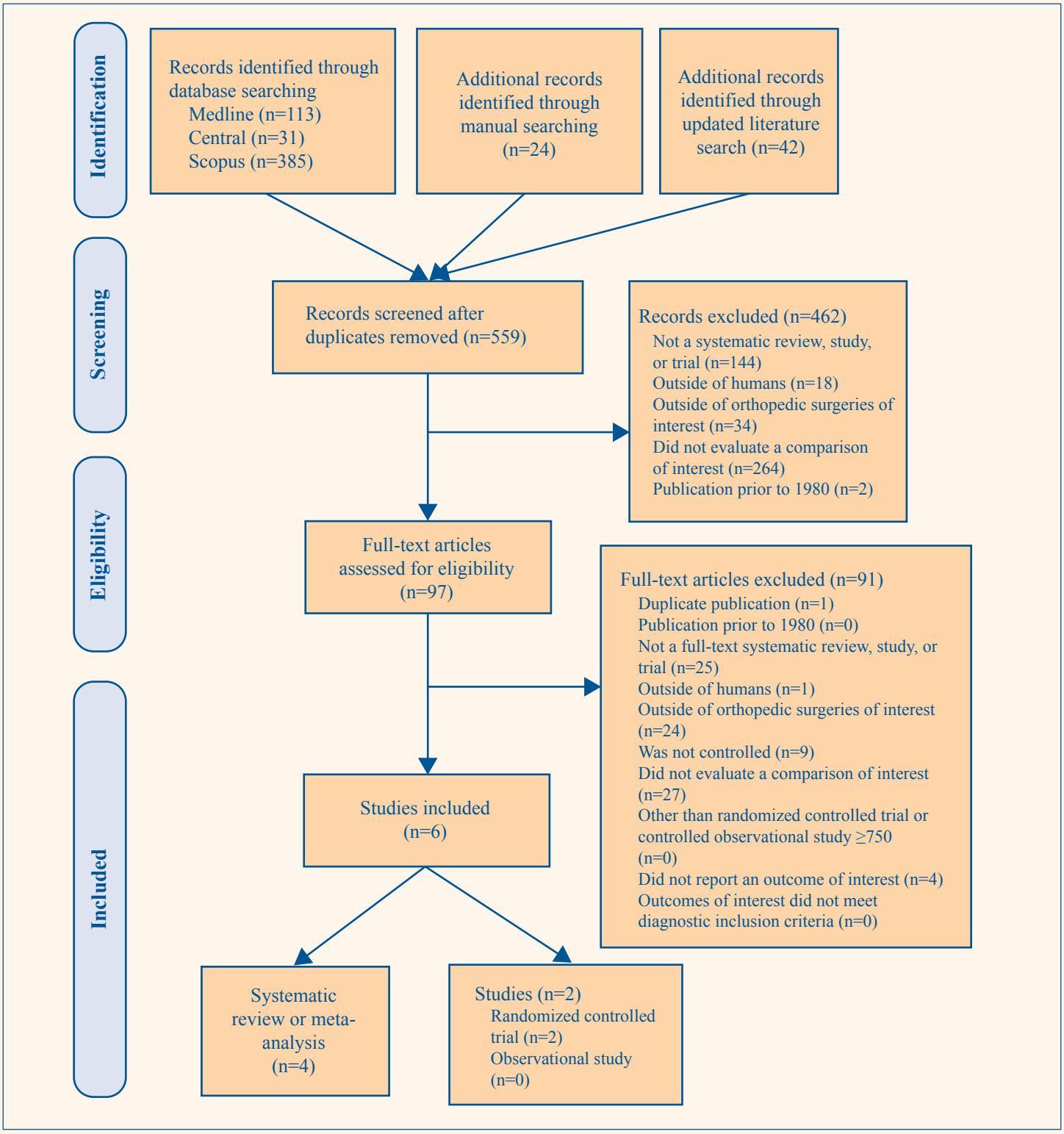


Table A. Summary of results from base case analyses in patients who had major orthopedic surgery*[6]

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

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

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 2. Impact of patient characteristics on outcomes – congestive heart failure					
Symptomatic objectively confirmed VTE	2 OBS	No	Significantly increases odds.	M	M
KQ 2. Impact of patient characteristics on outcomes – age					
Symptomatic objectively confirmed VTE	2 OBS	No	No significant impact.	L	M
DVT	3 OBS	No	Significantly increased risk.	L	L
KQ 4–8. Symptomatic objectively confirmed VTE					
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.70 (0.48 to 1.02).	L	M
LMWH vs. VKA	2 RCTs	Yes	No significant difference, OR 1.00 (0.69 to 1.46).	L	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.38 (0.19 to 0.77), NNT 8 to 54.	M	L
KQ 4–8. Major VTE					
Pharmacologic vs. no prophylaxis	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.21 (0.05 to 0.95), NNT 19 to 22.	L	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.26 (0.98 to 1.62).	M	L
KQ 4–8. Major PE					
Pharmacologic vs. no prophylaxis	12 RCTs	Yes	No significant difference, OR 0.38 (0.13 to 1.07).	L	L
LMWH vs. UFH	10 RCTs	Yes	Significantly decreased odds, OR 0.48 (0.24 to 0.95), NNT 8.	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.18 (0.41 to 3.39).	M	L
LMWH vs. VKA	5 RCTs	Yes	No significant difference, OR 1.11 (0.57 to 2.19).	M	M
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.23 (0.56 to 18.98).	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34).	L	M
Prolonged vs. standard duration prophylaxis	6 RCTs 1 RCT	Yes No	Significantly decreased odds, OR 0.13 (0.04 to 0.47), NNT 24 to 232.	H	L
KQ 4–8. Fatal PE					
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.90 (0.38 to 2.13).	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 1.43 (0.08 to 24.82).	L	L

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

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Nonfatal PE					
Pharmacologic vs. no prophylaxis	6 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 0.21 (0.04 to 1.30). Observational data were supportive.	L	L
LMWH vs. UFH	10 RCTs	Yes	No significant difference, OR 0.50 (0.25 to 1.00).	L	L
LMWH vs. FXaI	5 RCTs	Yes	No significant difference, OR 0.68 (0.34 to 1.37).	M	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, OR 0.93 (0.23 to 3.66).	L	L
LMWH vs. VKA	3 RCTs	Yes	No significant difference, OR 1.00 (0.20 to 4.95).	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 3.27 (0.56 to 18.98).	L	L
Pharmacologic + mechanical vs. pharmacologic	2 RCTs	Yes	No significant difference, OR 1.03 (0.14 to 7.34).	L	M
Prolonged vs. standard duration prophylaxis	5 RCTs 1 RCT	Yes No	Significantly decreased odds, OR 0.13 (0.03 to 0.54), NNT 58. One trial ineligible for pooling showed OR 0.13 (0.01 to 2.06).	M	L
KQ 4–8. Mortality					
Pharmacologic vs. no prophylaxis	10 RCTs 3 OBS	Yes (RCT)	No significant difference, OR 1.23 (0.54 to 2.78). One observational study supported this finding but another study suggested a decrease in the number of deaths with prophylaxis.	M	L
LMWH vs. UFH	8 RCTs	Yes	No significant difference, OR 0.39 (0.10 to 1.49).	M	L
LMWH vs. FXaI	5 RCTs 2 OBS	Yes (RCT)	No significant difference, OR 1.08 (0.72 to 1.60). One observational study suggested a significantly higher percent of deaths in patients who received LMWH vs. factor Xa inhibitors while the other study suggested no significant difference.	M	L
LMWH vs. DTI	4 RCTs	Yes	No significant difference, RR 0.45 (0.15 to 1.36).	M	L
LMWH vs. VKA	6 RCTs	Yes	No significant difference, OR 0.79 (0.42 to 1.50).	M	M
LMWH vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.31 (0.05 to 1.80).	L	L
UFH vs. DTI	2 RCTs	Yes	No significant difference, OR 7.13 (0.74 to 68.80).	L	L
KQ 4–8. DVT					
Pharmacologic vs. no prophylaxis	17 RCTs	Yes	Significantly decreased risk, RR: 0.56 (0.47 to 0.68), NNT 3 to 33.	M	L
Antiplatelet vs. mechanical	2 RCTs	Yes	Significantly increased risk, RR 1.63 (1.11 to 2.39), NNH 4 to 27.	M	L
LMWH vs. UFH	13 RCTs 1 RCT (2 comp)	Yes Yes	Significantly decreased risk, RR 0.80 (0.65 to 0.99), NNT 12 to 100. 1 trial ineligible for original pooled analysis showed RR 3.37 (0.70 to 16.17).	M	L

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

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. DVT (continued)					
LMWH vs. FXaI	5 RCTs	Yes	Significantly increased risk, RR 1.99 (1.57 to 2.51), NNH 13 to 26.	M	L
LMWH vs. VKA	5 RCTs	Yes	Significantly decreased risk, RR 0.66 (0.55 to 0.79), NNT 6 to 13.	L	M
LMWH vs. mechanical	3 RCTs	Yes	No significant difference, RR 0.90 (0.71 to 1.14).	M	L
UFH vs. DTI	2 RCTs	Yes	Significantly increased risk, RR 2.31 (1.34 to 4.00), NNH 5 to 11.	M	L
VKA vs. mechanical	3 RCTs	Yes	No significant difference, RR 1.45 (0.75 to 2.82).	L	L
Enoxaparin vs. other LMWH	2 RCTs	Yes	No significant difference, RR 1.05 (0.64 to 1.71).	L	L
IPC vs. GCS	1 RCT (2 comp)	Yes	Significantly decreased risk, RR 0.06 (0.01 to 0.41), NNT 3 to 7.	L	L
Pharmacologic + mechanical vs. pharmacologic	3 RCTs 1 RCT	Yes No	Significantly decreased risk, RR 0.48 (0.32 to 0.72), NNT 3 to 67. One trial ineligible for pooling showed RR 0.09 (0.01 to 0.85), NNT 5.	M	M
Prolonged vs. standard duration prophylaxis	7 RCTs 1 RCT	Yes No	Significantly decreased risk, RR 0.37 (0.21 to 0.64), NNT 5 to 32. One trial ineligible for pooling showed RR 0.61 (0.38 to 0.97).	M	M
KQ 4–8. Asymptomatic DVT					
Pharmacologic vs. no prophylaxis	3 RCTs	Yes	Significantly decreased risk, RR 0.52 (0.40 to 0.69), NNT 4 to 6.	M	L
LMWH vs. UFH	2 RCTs	Yes	No significant difference, RR 0.70 (0.43 to 1.16).	L	L
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 0.97 (0.85 to 1.10).	M	M
Prolonged vs. standard duration prophylaxis	4 RCTs	Yes	Significantly decreased risk, RR 0.48 (0.31 to 0.75), NNT 8 to 65.	H	L
KQ 4–8. Symptomatic DVT					
Pharmacologic vs. no prophylaxis	4 RCTs 1 OBS	Yes (RCT)	No significant difference, OR 1.07 (0.25 to 4.52). Observational study data were supportive.	M	L
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.62 (0.22 to 1.75).	L	L
LMWH vs. FXaI	6 RCTs	Yes	No significant difference, OR 0.48 (0.21 to 1.21).	M	M
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 0.98 (0.34 to 2.87).	M	L

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

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

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

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

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

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Major bleeding leading to reoperation					
LMWH vs. FXaI	4 RCTs	Yes	No significant difference, OR 0.67 (0.28 to 1.61).	M	L
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR 1.27 (0.43 to 3.75).	M	L
UFH vs. DTI	2 RCTs	No	No significant difference, one trial had no events and the other trial showed OR 0.51 (0.10 to 2.55).	L	L
KQ 4–8. Minor bleeding					
Pharmacologic prophylaxis vs. no prophylaxis	6 RCTs	Yes	Significantly increased risk, RR 1.67 (1.18 to 2.38), NNT 30 to 75.	H	M
LMWH vs. UFH	5 RCTs	Yes	No significant difference, RR 0.90 (0.63 to 1.28).	M	L
LMWH vs. FXaI	2 RCTs	Yes	Significantly decreased odds, OR 0.57 (0.35 to 0.94), NNT 31 to 60.	L	
LMWH vs. DTI	3 RCTs	Yes	No significant difference, RR: 1.07 (0.89 to 1.29).	M	L
LMWH vs. VKA	7 RCTs 1 RCT (2 comp)	Yes Yes	Significantly increased risk, RR 1.23 (1.06 to 1.43), NNH 18 to 218. One trial ineligible for the original pooled analysis showed a RR 1.49 (0.30 to 7.37) on days 0–1 and a RR 0.87 (0.37 to 2.06) on days 2–8.	M	M
VKA vs. mechanical	2 RCTs	Yes	No significant difference, OR 0.80 (0.26 to 2.41).	L	L
Prolonged vs. standard duration prophylaxis	3 RCTs	Yes	Significantly increased odds, OR 2.44 (1.41 to 4.20), NNH 11 to 118.	H	M
KQ 4–8. Surgical site bleeding					
LMWH vs. UFH	3 RCTs	Yes	No significant difference, OR 0.92 (0.46 to 1.82).	L	L
LMWH vs. VKA	2 RCT	Yes	Significantly increased odds OR 2.63 (1.31 to 5.28), NNH 23 to 64.	L	L
Enoxaparin vs. other LMWH	2 RCT	Yes	No significant difference, RR 1.35 (0.30 to 5.97).	L	L
KQ 4–8. Bleeding leading to transfusion					
LMWH vs. DTI	2 RCTs	Yes	No significant difference, RR 1.00 (0.59 to 1.69).	H	L
KQ 4–8. HIT					
LMWH vs. UFH	3 RCTs	Yes	Significantly decreased odds, OR 0.12 (0.03 to 0.43), NNT 34 to 202.	M	L

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

Endpoint/ Comparison	Type and Number of Studies	Pooled	Conclusion/Result	SOE	AOE
KQ 4–8. Readmission					
LMWH vs. UFH	2 RCT	Yes	No significant difference, RR 0.82 (0.20 to 3.38).	L	L
LMWH vs. mechanical	2 RCT	Yes	No significant difference, OR 0.83 (0.22 to 3.11).	L	L
Prolonged vs. standard duration prophylaxis	1 RCT (2 comp)	Yes	No significant difference, RR 0.29 (0.06 to 1.34).	L	L

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

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

Discussion

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

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

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

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

Addendum

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

Glossary

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

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

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

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

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

I^2: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

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

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

Other Orthopedic Surgery: Knee arthroscopy, surgical repair of a lower extremity injury distal to the hip (open reduction internal fixation of the femur, tibia, ankle or foot, intermedullary fixation, ankle fusion, osteotomy of the tibia or femur, open ligament reconstruction of the knee or ankle, and tendon repair) or elective spine surgery (anterior or posterior spinal fusion +/- decompression, laminectomy, or 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 1 indicates no difference in the odds between the two groups. Peto's odds ratios are used to compare two groups when the number of events is rare.

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

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

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

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

Standard Deviations (SDs): A measure of the variability of a dataset. For a simple dataset with numbers, can be calculated using the following formula:

$$\sigma = ((\sum(x-x_m))^2/N)^{0.5}$$

where σ is standard deviation, x_m is the average, $\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x, N is the total number of values.

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

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

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

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

References

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Full Report

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