



Effective Health Care Program

Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

Executive Summary

Introduction

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

Purpose of Review

Assess venous thromboembolism (VTE) prevention interventions with total hip replacement (THR), total knee replacement (TKR), and hip fracture (HFx) surgeries.

Key Messages

- Few head-to-head treatment comparisons have sufficient evidence. Most studies evaluated low molecular weight heparin (LMWH), not low-risk interventions (such as aspirin and mechanical devices); most reported on total deep vein thrombosis (DVT), an outcome that includes asymptomatic DVT and is thus of unclear clinical value.
- In THR, LMWH has lower VTE and adverse event risks than unfractionated heparin; LMWH and aspirin have similar risks of VTE and major bleeding; direct thrombin inhibitors (DTI) have lower DVT risk than LMWH but higher major bleeding risk; and higher dose LMWH has lower DVT risk but higher major bleeding risk than lower dose.
- In TKR, vitamin K antagonists have higher DVT risk than LMWH but lower major bleeding risk; and higher dose DTI has lower DVT risk but higher major bleeding risk than lower dose.



A variety of strategies to prevent VTE are available, including pharmacological (antiplatelet, anticoagulant) and mechanical devices.¹ Pharmacologic prophylactic treatments include unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKA), antithrombin III-mediated selective factor Xa inhibitors, direct factor Xa inhibitors (FXaI), bivalent and univalent direct thrombin inhibitors (DTI), and antiplatelet agents (such as aspirin). Mechanical prophylaxis aims to minimize stasis, the principal putative factor resulting in venous thrombosis; it may also stimulate fibrinolysis, another mechanism to limit thrombosis. It can be dynamic and intermittent (e.g., intermittent pneumatic compression device [IPC]) or static (e.g., graduated compression stockings [GCS]). The modalities can be used alone or in combination, at variable doses (of drugs) or regimens (of mechanical devices; e.g., different pressure or compression frequency), and for different durations. However, prophylaxis with pharmacologic strategies also has important potential harms (risks) including major bleeding, prosthetic joint infections, and the need for reoperation, which may all lead to major morbidities, death, permanent removal of the prosthetic joint, and increased hospital length of stay and costs.⁷ Postoperative bleeding and hematoma formation are considered direct risk factors for the development of prosthetic joint infections.⁸ Reoperation is frequently required for debridement with or without removal of the infected prosthesis. Following removal of an infected prosthesis and extended intravenous antibiotic treatment, further surgery may be required to either implant a new prosthesis or perform an arthrodesis of the joint. Mechanical devices (when used alone), however, are thought to be inferior to pharmacological agents to prevent VTE.

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

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

Scope

The 2012 Comparative Effectiveness Review on Venous Thromboembolism Prophylaxis in Orthopedic Surgery¹³ (hereafter “the 2012 VTE report”) addressed many of the uncertainties in this area, including questions regarding the natural history of VTE, predictors of VTE, and the likelihood that DVTs result in PE in patients undergoing THR, TKR, or Hfx surgery; the comparative efficacy of VTE prophylaxis strategies with no VTE prophylaxis, within and between classes of VTE prophylaxis modalities, and duration of VTE prophylaxis in patients undergoing these surgeries; and the efficacy of VTE prophylaxis in nonmajor orthopedic surgeries (knee arthroscopy, surgical repair of lower extremity injuries distal to the hip, and elective spine surgery). The 2012 VTE report included studies published from 1980 through May 2011. It found a general dearth of evidence regarding important clinical outcomes (nonfatal PE, fatal PE, major bleeding, reoperation), but high strength of evidence (SoE) that pharmacologic VTE prophylaxis reduces the risk of DVT compared to no VTE prophylaxis and increases the risk of minor bleeding. Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical prophylaxis reduced the risk of VTE, including, specifically, DVT. The comparisons of different classes of VTE prophylaxis modalities (e.g., different pharmacologic classes or pharmacologic versus mechanical devices) provided neither adequate evidence for important clinical outcomes nor strong evidence for other outcomes, including DVT. There were few studies evaluating the new FXaIs. In general, different interventions within classes were not statistically significantly different in their effects on DVT or bleeding. There was not strong evidence for other Key Questions.

We conducted a surveillance review of new studies potentially eligible to update all Key Questions from the 2012 VTE report. The surveillance review is summarized in the online protocol for this review.¹⁴ Upon discussion of the current state of the evidence with a panel of technical experts, we determined that a focused update of the 2012 Agency for Healthcare Research and Quality (AHRQ)

report would be of greatest value. Based on their input and the findings of the surveillance review, we focused the update on comparisons between specific prophylaxis interventions; different classes of intervention; different doses, regimens, and treatment durations of interventions; different combinations of interventions; and different timing of starting prophylaxis (in relation to the time of surgery).

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

Key Questions

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

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

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

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

KQ 4 (update of original KQ 7 plus expansion): In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture

surgery), what is the comparative efficacy of combined classes of thromboprophylaxis interventions versus single classes on venous thromboembolism outcomes, treatment adherence, major bleeding, and other adverse events?

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

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

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

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

Methods

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

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the KQs that have been published since the 2012 VTE report, which included studies published from 1980 through May 2011. We searched PubMed®, both the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and Embase® databases. Searches were limited to January 2010 through June 3, 2016. We included an overlap of more than 1 year with the search done for the 2012 VTE report. The updated literature searches replicated the searches from the 2012 VTE report and added additional

terms for new treatments (e.g., factor Xa inhibitors [FXaI]). The search strategy was peer reviewed by an independent, experienced information specialist/librarian.

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

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

Study Eligibility Criteria

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

Populations of Interest

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

Interventions of Interest

The interventions of interest for all KQs included pharmacological VTE prophylaxis agents within the defined classes of antiplatelet agents, low molecular

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

Comparators of Interest

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

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

Outcomes of Interest

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

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

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

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

We included confirmed and unconfirmed VTE, but downgraded the risk of bias for those studies that analyzed unconfirmed VTE. If both confirmed and unconfirmed VTE were reported, we extracted only the confirmed VTE data.

Eligible Study Designs

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

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

Timing

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

Setting

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

Study Selection

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

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

Data Extraction

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

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

Risk of Bias Assessment

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

Data Synthesis

Pairwise Meta-Analysis

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

Network Meta-Analysis

To address KQ 5, we conducted network meta-analyses under a Bayesian framework. The specific model is described by Dias et al.²¹ Network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct comparisons (where interventions are compared head-to-head) and indirect comparisons (where

interventions are compared through other reference interventions). Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that there is consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is similar across trials, and thus, patients are similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons (where the direct and indirect comparisons contradict each other).

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

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach.²³ This approach evaluates each treatment comparison in terms of its direct and indirect evidence estimates. Discrepancies between these estimates indicate inconsistency. Since we did not find any evidence of inconsistency, only results from the (consistency) network meta-analysis are presented. However, the inability of the models to detect inconsistency in our evidence base with sparse data may be due to the lack of power rather than suggestive of consistent networks.

We conducted a total of 12 network meta-analyses to compare all treatment alternatives across studies. For each of three surgeries (THR, TKR, and HFX surgery) and for the two outcomes (total DVT and major bleeding) we conducted two analyses: 1) comparisons of classes of thromboprophylaxis interventions (e.g., LMWH,

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

Summarizing Findings Across Studies

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

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

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

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

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

Subgroup Analyses and Metaregression

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

Grading the Strength of Evidence

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

provide at least low SoE). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating are summarized in a “Strength of Evidence” table detailing our reasoning for arriving at the overall SoE rating.²⁴

Peer Review

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

Results

Summary of Studies

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

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

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

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

Randomized Controlled Trials

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

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

^aThe current review assessed risk of bias domains not consistently addressed by the 2012 VTE report. We did not assess these studies for these risk of bias domains, but instead marked them as “not reported”.

Nonrandomized Comparative Studies

Overall, we included 15 NRCSs. Five NRCSs evaluated only THR, six only TKR, three had separate analyses of THR and TKR, and one evaluated HFX surgery. Two reported industry funding, and the other 12 NRCSs explicitly reported no industry support. In general, the risk of bias was low for incomplete results reporting (2 unclear) and timing of outcome assessments (3 unclear). One NRCS had high risk of bias for adverse event reporting and one was unclear. Similarly, one NRCS had high risk of bias for compliance with interventions and a second was unclear. One NRCS had high risk of bias for patient selection, and a second was unclear. Seven NRCSs had high risk of bias for group similarity at baseline (4 unclear); five for assessment of outcomes (4 unclear). Seven NRCSs had high risk of bias for blinding of outcome assessors, and another five were unclear. Eight had high risk of bias for selective outcome reporting.

Correlation of DVT and PE Across Trials

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

Key Question 1: Comparison of Thromboprophylaxis Intervention Classes

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

Total Hip Replacement

Key Points

- There were 46 RCTs and 5 NRCSs that compared classes of interventions in patients undergoing THR.
- Pairwise comparisons between classes had sufficient data for only six pairs of classes.
 - LMWH vs. DTI: Across outcomes there is a tradeoff between the two drug classes. Moderate SoE favors DTI to prevent total DVT and, separately, proximal DVT, but low SoE favors LMWH to avoid major bleeding.
 - LMWH vs. FXaI: Across outcomes, the evidence is inconsistent. The studies found that FXaI better lowers the risk of total VTE (low SoE), total DVT (moderate SoE), and proximal DVT (moderate SoE), but LMWH better lowers the risk of symptomatic VTE (low SoE) and symptomatic DVT (low SoE). There was high SoE that LMWH is better to prevent major bleeding, but both classes were similar in rates of study-defined serious adverse events (moderate SoE). The inconsistencies in these findings suggest important reporting bias.
 - LMWH vs. UFH: Overall, favors LMWH, with lower risk of total PE (high SoE), proximal DVT (moderate SoE), and major bleeding (moderate SoE); risk of total DVT was similar between drug classes (moderate SoE).
 - LMWH vs. VKA: Overall unclear. There is insufficient evidence regarding the relative benefit of either drug class to lower the risk of any VTE outcome, but VKA results in lower risk of major bleeding (high SoE).
 - LMWH vs. aspirin: Based primarily on a very large propensity-score-adjusted NRCS, LMWH and aspirin result in similar rates of total PE, symptomatic DVT, and major bleeding (all low SoE).
 - Mechanical devices vs. VKA: Overall, unclear. VKA results in lower risk of proximal DVT (high SoE), but insufficient evidence all favors mechanical devices to lower the risk of total DVT, and adverse events data have not been reported.
- For all other class comparisons and outcomes there was insufficient evidence.
- Although studies reasonably should have had data for all VTE-related outcomes and for major bleeding and other serious adverse events, most outcomes

were not reported by many studies, resulting in a high risk of reporting bias across the evidence base.

- A within-study subgroup analysis by chronic kidney disease category was inconclusive regarding differential risks of bleeding with LMWH and DTI.
- Industry-funded studies had similar finding as other studies. Asian studies had similar findings as non-Asian studies.

Summary Results for THR Studies

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

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

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

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

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

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

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

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

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

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

Table A. Total hip replacement, intervention class versus class: Summary of “sufficient” evidence (continued)

Comparison	Outcome*	Design: No. Studies (N)	Summary OR (95% CI) or Range of Estimates†	Conclusions	SoE Grade
LMWHvs. aspirin	PE, total	NRCS: 2 (110,117)	0.94 (0.75, 1.17)	Either	Low
	DVT, symptomatic	NRCS: 1 (108,584)	0.84 (0.70, 1.03)	Either	Low
	Bleeding, major	NRCS: 1 (108,584)	0.95 (0.77, 1.17)	Either	Low
	VTE vs. AE‡ (reported)	NRCS: 2 (110,117)		<i>Either: Similar VTE outcomes and major bleeding with LMWH and aspirin.</i>	
Mechanical Devices vs. VKA	DVT, proximal	RCT: 3 (434)	Range 2.39 to 4.69†	Favors VKA	High

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

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

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

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

Subgroup Analysis in THR Studies

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

were the same (0.3% in both arms). For chronic kidney disease categories 1-2 (n=700), DVT rates were lower in the enoxaparin arm (0.6% vs. 0%).

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

bleeding history or on antithrombotic medication). Thus, across-study comparisons of subgroup factors are limited.

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

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

Total Knee Replacement

Key Points

- There were 29 RCTs and 6 NRCSs that compared classes of interventions in patients undergoing TKR.
- Pairwise comparisons between classes had sufficient data for meta-analyses for only two pairs of classes.
 - LMWH vs. FXaI: Overall, the evidence is unclear. FXaI results in a lower risk of total VTE (low SoE), total DVT (low SoE), and proximal DVT (moderate SoE), but similar risks for total VTE (moderate SoE)

and symptomatic DVT (low SoE); risk of major bleeding is lower with LMWH (low SoE) but risk of study-defined serious adverse events is lower with FXaI (low SoE).

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

Summary Results for TKR Studies

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

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

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

Other intervention classes compared by fewer studies (with insufficient evidence) included antiplatelet drug versus FXaI (1 RCT), antiplatelet drug versus mechanical devices (1 RCT, 1 NRCS), antiplatelet drug (aspirin) versus VKA (1 RCT), DTI versus FXaI (1 RCT), LMWH versus antiplatelet drug (1 RCT), LMWH versus FXIi (1

RCT), LMWH versus mechanical devices (1 RCT and 1 NRCS), LMWH versus UFH (2 RCTs), and VKA versus mechanical devices (1 NRCS). Five RCTs evaluated LMWH vs. DTI but had highly inconsistent findings

related to symptomatic DVT (3 RCTs) and rare episodes of major bleeding resulting in a highly imprecise effect estimate (5 RCTs).

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

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

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

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

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

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

Subgroup Analysis in TKR Studies

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

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

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

For the comparison of Asian versus non-Asian RCTs, only the comparison of LMWH versus FXaI was analyzable. For total DVT, no significant difference (P=0.97) was found between the four Asian studies (summary OR 2.15, 95% CI 1.35 to 3.41) and three non-Asian studies (summary OR 2.12, 95% CI 1.59 to 2.82) by random effects model metaregression. However, the total DVT rate was lower in the Asian RCTs (9.6%) than the non-Asian

studies (16.0%, P<0.01). Similarly, for major bleeding, no significant difference (P=0.34) was found between the two Asian studies (summary OR 0.27, 95% CI 0.03 to 2.32) and the five non-Asian studies (OR 0.89, 95% CI 0.29 to 2.72). Major bleeding rates were similar between Asian studies (0.7%) and non-Asian studies (0.9%, P=0.57).

Hip Fracture Surgery

Key Points

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

Summary Results for Hfx Studies

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

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

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

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

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

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

Key Question 2: Comparison of Within-Class Thromboprophylaxis Interventions

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

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

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

Key Points

- There were 22 RCTs and 2 NRCSs that compared different intervention doses or durations in patients undergoing THR, 18 RCTs and 1 NRCS in patients undergoing TKR, and 2 RCTs in patients undergoing Hfx surgery.

- Only a small number of drug (or class) dose or duration comparisons had sufficient data.
 - THR
 - ♦ FXaI low vs. high dose: Overall, the evidence is unclear. There is low SoE that higher dose FXaI (darexaban 30 to 60 mg, edoxaban 30 mg) has a lower risk of total VTE than lower dose FXaI (darexaban 10 to 15 mg, edoxaban 15 mg), but there is insufficient evidence for other outcomes, including adverse events.
 - ♦ LMWH low vs. high dose: There is evidence of a tradeoff between low and high dose LMWH. Higher dose LMWH (e.g., enoxaparin 40 mg) results in a lower risk of total DVT than lower dose LMWH (e.g., enoxaparin 20 to 30 mg) (low SoE), but both high and low dose LMWH result in similar risk of proximal DVT. Lower dose LMWH has a lower risk of major bleeding than higher dose LMWH (moderate SoE).
 - ♦ LMWH short vs. long duration: The evidence supports longer duration LMWH. Longer duration LMWH (>2 weeks) results in lower risk of total PE (low SoE), total DVT (high SoE), and proximal DVT (moderate SoE) than shorter duration LMWH (up to 10 days or to hospital discharge); bleeding events were rare in the

LMWH studies yielding insufficient evidence regarding relative difference in risk.

- TKR
 - ◆ DTI low vs. high dose: There is evidence of a tradeoff between low and high dose DTI. Higher dose DTI (dabigatran 220 to 225 mg) has a lower risk of total DVT (high SoE) and proximal DVT (moderate SoE) than lower dose (dabigatran 150 mg), but lower dose DTI has less risk of major bleeding (low SoE)
 - ◆ FXaI low vs. high dose: Overall, the evidence is unclear. Higher dose FXaI (e.g., edoxaban 60 mg, darexaban 30 mg) results in a lower risk of total VTE (moderate SoE), symptomatic DVT (low SoE), and proximal DVT (low SoE) than lower dose FXaI (e.g., edoxaban 5 mg, darexaban 15 mg); however, there was insufficient evidence for adverse events.
- HFx surgery
 - ◆ Data were insufficient to summarize the evidence for different dose or duration of interventions for HFx surgery

Summary Results for Key Question 3

More than 300 specific comparisons of different drug doses or device regimens have been reported; the large majority of specific comparisons were made by a single study only. Comparisons with sufficient evidence are summarized here. These all pertain to class-level

analyses; comparisons of individual thromboprophylaxis interventions within classes were not evaluated with sufficient frequency to allow a conclusion of sufficient evidence.

Total Hip Replacement

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

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

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

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

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

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

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

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

Total Knee Replacement

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

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

Table E. Total knee replacement, comparison of different doses or treatment durations: Summary of “sufficient” evidence

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

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

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

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

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

Hip Fracture Surgery

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

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

Key Points

- There were 7 RCTs and 2 NRCSs that compared single versus combined classes of intervention in patients undergoing THR, 8 RCTs and 3 NRCSs in patients undergoing TKR, and no studies in patients undergoing Hfx surgery.

- Overall, there was insufficient evidence regarding the differences between combined or single classes of interventions to prevent VTE overall or avoid adverse events.

Summary Results for Key Question 4

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

For THR, RCTs provided insufficient evidence for comparisons of antiplatelet drug versus antiplatelet drug and mechanical device; LMWH alone versus combinations of LMWH and antiplatelet drug, DTI, FXaI, and

mechanical device; mechanical device alone versus the mechanical device and antiplatelet drug, both antiplatelet drug and UFH, and VKA; and UFH alone versus combination UFH and LMWH. In addition, one RCT compared combination antiplatelet drug and UFH versus combination antiplatelet drug, UFH, and mechanical device.

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

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

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

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

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

Key Points

- Conclusions from all network meta-analyses are limited due to the sparseness of direct comparisons between most interventions within each network.
- Conclusions are also limited because there were sufficient data to allow network meta-analyses only for total DVT and major bleeding, not other, clinically significant, VTE outcomes or adverse events.

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

- For patients undergoing either **HFx surgery**, network meta-analysis suggests that comparisons between specific pairs of classes or of interventions were too sparse to yield sufficient conclusions regarding risks of **total DVT or major bleeding**.

- **By class**

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

- **By class**

- ♦ There were 8 RCTs that compared specific interventions for total DVT and 6 for major bleeding, but there were insufficient data to draw conclusions.

Total Hip Replacement

Total Deep Vein Thrombosis

Comparison of Classes by Network Meta-Analysis in THR Studies

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

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

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

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

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

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

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

Major Bleeding

Comparison of Classes by Network Meta-Analysis in THR Studies

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

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

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

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

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

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

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

Total Knee Replacement

Total Deep Vein Thrombosis

Comparison of Classes by Network Meta-Analysis in TKR Studies

There were 31 RCTs that evaluated interventions in at least two classes and reported total DVT after TKR. Across this study set, 12 classes were evaluated (antiplatelet drug [aspirin], antiplatelet drug plus mechanical device, DTI, FXaI, FXaI plus mechanical devices, FXIi, LMWH, LMWH plus mechanical device, mechanical devices, UFH, VKA, placebo). Of the 66 possible pairwise comparisons,

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

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

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

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

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

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

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

Major Bleeding

Comparison of Classes by Network Meta-Analysis in TKR Studies

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

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

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

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

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

with each of 13 other interventions; most frequently with dabigatran (5 RCTs). The combination of edoxaban plus VFP was directly compared with edoxaban only.

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

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

Hip Fracture Surgery

Total Deep Vein Thrombosis

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

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

There were no statistically significant differences. Overall, FXaI and UFH were likely to be among the top two interventions whereas placebo and LMWH were likely to be among the bottom two interventions. However, data were sparse and only LMWH was directly compared to more than two other interventions by at least two RCTs each (for two comparisons).

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

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

Enoxaparin was the most common comparator, being directly compared with five other interventions. UFH was directly compared with dalteparin only.

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

Major Bleeding

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

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

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

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

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

There were no statistically significant differences. Overall, aspirin had the highest probability of being among the top three interventions (>99%) to avoid major bleeding

with thromboprophylaxis after HFX surgery, followed by placebo (95%) and warfarin (94%). The interventions likely to be among the bottom three interventions were fondaparinux (82%), semuloparin (77%), and enoxaparin (67%). However, only enoxaparin and fondaparinux were directly compared by two RCTs, with similar risk of major bleeding.

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

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

Discussion

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

A large volume of evidence has been garnered comparing intervention options to prevent VTE in patients undergoing THR, TKR, and HFX surgery. In total this systematic review addressing comparative effectiveness and harms of drug and mechanical interventions included 127 RCTs and 15 large NRCSSs examining head-to-head comparisons. The review explicitly evaluates direct comparative information and does not examine placebo-controlled effectiveness studies (with the exception of including placebo trials in the network meta-analyses). These studies pertain to three different surgeries and include nine different classes of intervention and 21 specific interventions (plus 6 combinations of classes or interventions). Furthermore, the studies disproportionately (78%) evaluated LMWH and enoxaparin in particular (60%). Thromboprophylactic interventions that are most likely to have lower risk of major bleeding (particularly aspirin and mechanical

devices, for which there is limited research funding support compared with newer pharmaceutical interventions) have been inadequately studied in direct comparison studies, severely limiting strong conclusions regarding their relative effectiveness and safety. In addition, studies implicitly used a variety of specific orthopedic surgical techniques, but generally failed to describe these sufficiently to allow cross-study comparisons based on surgical techniques (or VTE- or bleeding-risk status of patients); no study reported within-study comparisons of different patients based on these characteristics. Studies also differed in regard to the specific VTE outcomes that were reported. Most studies reported total DVT (82%), which includes asymptomatic DVTs and is thus not routinely diagnosed and may not be clinically important as pertains to PE and other clinical vascular outcomes. Between one-third and two-thirds of studies did not report the other, more clinically important, VTE outcomes (e.g., symptomatic DVT). Based on an imperfect analysis across generally relatively small studies, we found that rates of total DVT are not correlated with rates of total PE ($r=0.07$); although, this analysis is also hampered by the fortuitous fact that few study participants had a PE. Because PEs are relatively rare, total DVTs have become a common primary outcome for VTE prophylaxis studies in part to increase power (since total DVTs are more common than symptomatic DVTs); however, reliance on this outcome may result in biased conclusions if some interventions are more effective at preventing asymptomatic or distal DVTs (and thus total DVTs) but not more effective at preventing clinically significant DVTs. Because of (potentially biased) incomplete reporting of all VTE outcomes, it is not possible to assess whether total DVT is an appropriate proxy for PE, death, or long-term sequelae secondary to DVTs.

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

with LMWH versus VKA, and the superiority of longer duration LMWH than shorter duration.

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

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

Evidence Summary

Total Hip Replacement

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

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

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

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

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

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

- Dalteparin is most likely to be most effective to prevent total DVTs compared with enoxaparin, IPC, UFH, and warfarin (moderate SoE)

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

Total Knee Replacement

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

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

From network meta-analyses,

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

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

finding as other studies. Asian studies had similar findings as non-Asian studies.

Hip Fracture Surgery

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

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

Evidence and Analysis Limitations

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

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

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

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

The RCTs were generally consistent in regard to their eligibility criteria, mostly including all-comers without contraindications. This approach improves the applicability of the individual trials (and thus of the systematic review). Nonetheless, effect sizes in subgroups were rarely reported in these RCTs, and it greatly hampered our ability to evaluate potential explanations for heterogeneity or to hypothesize about possible subgroup differences based

on patient history or surgery or anesthesia characteristics. Other than funding source, we were able only to evaluate potential differences between Asian and non-Asian studies. Overall, we found no significant difference between studies conducted in different regions (among analyzable studies), except major bleeding for the comparison of LMWH and FXaI in patients undergoing THR (summary OR in Asian RCTs 1.95, 95% CI 0.46 to 8.22; summary OR in non-Asian studies 0.68, 95% CI 0.49 to 0.94). Nevertheless, the event rates in the Asian studies were generally lower than the non-Asian studies. It suggests incomparability in the two populations besides ethnicity, which might explain the potential difference in the treatment effects. Only two RCTs reported on within-study subgroup analyses based on chronic kidney disease category (major bleeding, enoxaparin vs. desirudin) and by unilateral versus bilateral TKR surgery (DVT, aspirin vs. compression boots). Neither study found a significant difference in treatment effect in the different subgroups. Differences in effectiveness and safety between numerous different subgroups could not be evaluated due to lack of reporting of such analyses, including by age, sex, race, thrombosis risk factors, bleeding risk factors, comorbidities, medication use, or surgery types or techniques.

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

Future Research Recommendations

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

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

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

submitting trial results to a publicly-accessible registry such as ClinicalTrials.gov.

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

Conclusions and Clinical Implications

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

Based on head-to-head comparisons for which there is sufficient evidence to make conclusions, LMWH is more effective to prevent VTE outcomes (with moderate to high SoE) and safer to prevent major bleeding (moderate SoE) than UFH (in patients undergoing THR). There are

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

Two other findings of note are that for both LMWH (in THR) and DTI (in TKR) there is variable SoE that higher dose LMWH or DTI is more effective to prevent DVT but lower doses result in less major bleeding. Evidence is insufficient regarding different doses of other drug classes, different durations of treatment, comparisons of specific interventions, evaluations of combinations of interventions, and comparisons of timing of when to start thromboprophylaxis.

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

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

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

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

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Full Report

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