Pharmacotherapy for Venous Thromboprophylaxis following Total Hip or Knee Arthroplasty: A Systematic Review and Network Meta-analysis

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Abstract

The optimal pharmacological prophylaxis for venous thromboembolism (VTE) after hip or knee arthroplasty is uncertain. We conducted a systematic review and network meta-analysis to compare the efficacy and safety of various medications. We searched multiple databases for randomized clinical trials (RCTs) comparing medications (including factor Xa inhibitors, factor IIa inhibitor, warfarin, unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], aspirin, pentasaccharide) for VTE prophylaxis post-arthroplasty. Outcomes included any postoperative VTE identified with screening, major bleeding, and death. We used LMWH as the main comparator for analysis and performed trial sequential analysis (TSA) for each pairwise comparison. Certainty of evidence was assessed using GRADE (Grading of Recommendations, Assessments, Developments and Evaluations). We analyzed 70 RCTs (55,841 participants). Factor Xa inhibitors decreased postoperative VTE significantly compared with LMWH (odds ratio [OR]: 0.55, 95% confidence interval [CI]: 0.44–0.68, high certainty). Pentasaccharides probably reduce VTE (OR: 0.61, 95% CI: 0.36–1.02, moderate certainty), while the factor IIa inhibitor dabigatran may reduce VTE (OR: 0.75, 95% CI: 0.40–1.42, low certainty). UFH probably increases VTE compared with LMWH (OR: 1.31, 95% CI: 0.91–1.89, moderate certainty), and other agents like warfarin, aspirin, placebo, and usual care without thromboprophylaxis increase VTE (high certainty). Factor Xa inhibitors may not significantly affect major bleeding compared with LMWH (OR: 1.06, 95% CI: 0.81–1.39, low certainty). No medications had a notable effect on

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- meta-analysis
- total hip or knee arthroplasty
- venous thromboembolism

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mortality compared with LMWH (very low certainty). TSA suggests sufficient evidence for the benefit of factor Xa inhibitors over LMWH for VTE prevention. Compared with LMWH and aspirin, factor Xa inhibitors are associated with reduced VTE after hip or knee arthroplasty, without an increase in bleeding and likely no impact on mortality.

Following elective total hip or knee arthroplasty (THA or TKA), patients have a higher risk of venous thromboembolism (VTE).[1–4] Symptomatic VTE rates in this setting can be as high as 3% without thromboprophylaxis, and 1.5% with thromboprophylaxis,[4–7] resulting in important morbidity, mortality,[8–10] and health care costs.[11–13] As more arthroplasties are being conducted over time,[14–16] there is a need for appropriate perioperative prophylaxis against thromboembolism informed by best possible evidence summaries.[11,17,18]

Several medications are available for postoperative VTE prophylaxis.[19,20] Various societies have suggested or recommended, with some variation, specific agent(s) for VTE prophylaxis.[19,21–25] Earlier guidelines[24,25] did not specify a recommended agent or duration of therapy, while more recent guidelines have recommended low-dose aspirin (though low-molecular-weight heparin [LMWH] and factor Xa inhibitors had similar efficacy),[26] or LMWH, pentasaccharide, non-vitamin K antagonist oral anticoagulants (NOACs: factor IIa inhibitor dabigatran, factor Xa inhibitors apixaban and rivaroxaban), low-dose unfractionated heparin (UFH), or vitamin K antagonists (VKAs).[23] All guidelines have been limited to weak recommendations and reported very low certainty in the current evidence,[22] highlighting an important knowledge gap.[20]

Prior systematic reviews and meta-analyses have investigated pharmacological thromboprophylaxis in smaller patient populations or intervention groups with unspecified treatment details. While other analyses have found that rivaroxaban was associated with the greatest reduction in deep vein thrombosis (DVT), they were limited by the patient population (only TKAs[27]), or by interventions (comparisons between NOACs and non-NOACs unclear[28]; exclusion of important interventions including aspirin, apixaban, edoxaban[29]). These analyses included a small number of randomized controlled trials (RCTs)[30,31] and included studies which report on doses or regimens of medications which fall outside of current treatment guidelines, which limits the applicability of their results. The aim of this systematic review and network meta-analysis was to summarize the efficacy and safety of pharmacological agents in patients following elective hip and knee arthroplasty.

Methods

Search Strategy and Selection Criteria

We registered this study with PROSPERO (CRD42022357206, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=357206) and conducted it in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement extension for Network Meta-analysis (►**Supplementary Table S1**).[32] With a medical information specialist, we searched MEDLINE, Embase, and Scopus databases from inception to 13 October 2023, using the following keywords: "knee arthroplasty" or "hip arthroplasty," "aspirin" or "heparin" or "direct oral anticoagulant," "venous thromboembolism" or "hemorrhage," and "randomized controlled trial" without any limitation for language (►**Supplementary Table S2**). We reviewed the reference lists of included studies and relevant review articles, searched clinicaltrials.gov for unpublished data or protocols, and used an artificial intelligence virtual research assistant ("Elicit"),[33] to obtain any additional studies.

Eligibility Criteria

We included RCTs comparing two or more medications, or a medication with a control or placebo as venous thromboprophylaxis following elective hip or knee arthroplasty, including LMWH (enoxaparin, dalteparin, nadroparin, and tinzaparin), factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), factor IIa inhibitor (dabigatran), aspirin, UFH, VKAs (warfarin), and pentasaccharide (fondaparinux), as well as placebo and no intervention (control). We excluded trials reporting on hybrid regimens (starting on one medication for a period of time before switching to another medication), animals or pediatric patients (<18 years old), and observational studies. In the case of overlapping patient data, we included the largest study and excluded any other overlapping studies.

Outcomes

Outcomes included VTE at the longest point of follow-up, bleeding based on the ISTH definition[34] (specifically, major bleeding events), and mortality at the last point of follow-up. If the total number of VTE was reported, we collected that data for analysis. However, if DVT and pulmonary embolism (PE) were reported separately, we combined the number of patients with DVT and PE based on radiological imaging or autopsy.[35]

Data Collection and Risk-of-Bias Assessment

We collected data using a prespecified data extraction form (►**Supplementary Table S3**). We recorded the event rates and total number of patients in each arm. Where appropriate, we derived the means and standard deviations from the aggregate data presented in each study as per Wan and colleagues.[36]

We assessed individual study risk of bias using the Cochrane Risk of Bias 2.0 tool for RCTs (RoB2.0).[37] We assessed certainty of evidence using the Grading of Recommendations, Assessments, Developments and Evaluations (GRADE) approach, which rates the certainty of evidence from "high" (we are confident that the true effect lies close to that of the estimate of the effect) to "very low" (we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the

estimate of effect).[38,39] We used informative narrative statements to communicate the certainty in the pooled estimates.[40] B.S.J.Y., R.R.L., R.L., and J.W.P. independently and in duplicate conducted two-staged screening of studies (titles and abstracts, followed by full texts), collected data, and assessed risk of bias using the systematic review management software Covidence (Melbourne, Australia); conflicts were resolved by consensus and discussion.

Data Synthesis

For all comparisons, we first conducted random-effects pairwise meta-analyses. In studies with null events, we applied a continuity correction of 0.5. We present outcomes as pooled odds ratios (ORs) with their corresponding 95% confidence intervals (CIs).

We assessed the feasibility for network meta-analysis by evaluating the availability of evidence, homogeneity of study designs, patients, and characteristics of interventions across the included studies (transitivity), the structural properties of the network (connectivity), and network coherence. We conducted frequentist random-effects network meta-analysis,[41,42] and visualized network geometry using a network graph. We used the thickness and depth of color of each edge to represent the number of studies in each pairwise comparison. We calculated the total network inconsistency based on the full design-by-treatment interaction random-effects model,[43] and assessed incoherence via the node splitting approach. We then estimated the ranking probabilities using the frequentist analogue of the Surface Under the Cumulative Ranking (SUCRA) curve based on 10,000 repetitions.[44]

We conducted several sensitivity analyses: we excluded studies with high risks of bias, combined placebo and control groups under a common node in the network, excluded studies published before 2000 to eliminate the possibility of changes in management over time, separated NOACs into their individual medications (rivaroxaban, apixaban, edoxaban, dabigatran), and stratified aspirin based on dose (low dose $\leq$ 325 mg, high dose $>$325 mg). We also conducted two subgroup analyses: the first separating the analysis of medications in hip and knee arthroplasties individually, and the second analyses studies that examined prespecified dosing regimens as per package inserts provided by their respective drug manufacturers versus those that did not (►**Table 1**). We tested for interaction between both types of surgery using the ratio of ORs.[45]

We assessed statistical heterogeneity (inconsistency) as part of the GRADE approach, using I-squared, tau-squares values, chi-squared test, and visual inspection of the forest plots.[46] We assessed for publication bias qualitatively using visual inspection of funnel plots. We conducted statistical analysis using R 4.1.2.

In addition, we conducted trial sequential analysis (TSA) for all outcomes to assess each pairwise comparison. The probability of false results increases as more statistical tests are applied to accumulated data.[47] Similar to RCTs, meta-analyses also have a "required information size" to ensure sufficient events and sample size. TSA combines cumulative meta-analysis with information size calculations to estimate the significance of the cumulative pooled estimate following the addition of a new trial,[47] reducing the rates of falsely significant results. We performed TSA using TSA v0.9.5.10 (www.ctu.dk/tsa) assuming a type I error of 5% and power of 80%, and used the relative risk reduction, control event proportion, and heterogeneity from each pairwise meta-analysis accordingly.

Results

Of 2,888 references, we reviewed 229 full texts. We included 70 RCTs (55,841 patients) (►**Fig. 1**).[5,48–116] A total of 22,663 (41.1%) patients were male, and the average age of the patients ranged between 43 and 73 years. In addition, 32,098 (57.7%) of the patients underwent hip arthroplasty while 23,543 (42.3%) of the patients underwent knee arthroplasty. ►**Supplementary Tables S4** to **S6** summarize further details of the included studies, and ►**Supplementary Table S7** presents the risk-of-bias judgments of the included studies.

Table 1 Medication doses for subgroup analysis

Class	Name	Dose
LMWH	Enoxaparin	30 mg SC every 12 hours or 40 mg SC OD
	Dalteparin[a]	2,500 IU SC for first 1 or 2 doses, then 5,000 IU SC OD
	Tinzaparin	50 or 75 IU/kg OD
Anti-Xa	Rivaroxaban	10 mg PO OD
	Apixaban	2.5 mg PO BD
Anti-IIa	Dabigatran[a]	110 mg PO on first day, then 220 mg PO OD
Pentasaccharide	Fondaparinux	2.5 mg SC OD
VKA	Warfarin	Adjusted PO dose to maintain a target INR of 2.5 (INR range: 2.0–3.0)
UFH		5,000 IU SC every 8 or 12 hours
Aspirin		All doses accepted

Abbreviations: BD, twice daily; INR, international normalized ratio; IU, international anti-factor Xa units; LMWH, low-molecular-weight heparin; OD, once daily; PO, per oral; SC, subcutaneous injection; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Approved for total hip arthroplasty only.

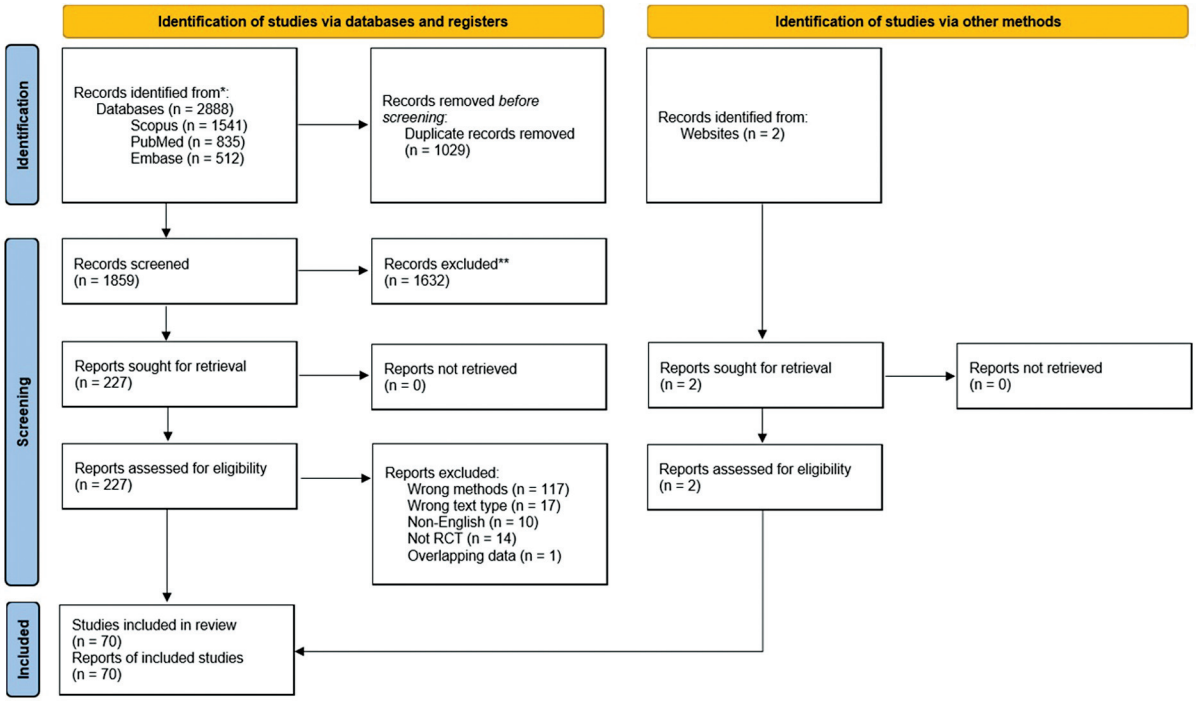

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

Assessment of Study Quality

►**Supplementary Table S7** summarizes the risk of bias of each individual RCTs. We judged three studies to have a high risk of bias (due to bias arising from the randomization process), 18 studies to be at moderate risk of bias (due to deviations from intended interventions and measurement of outcomes), and 49 to be low risk of bias.

Outcomes

Of 55,841 patients, 4,786 patients (8.6%) had VTE. Compared with LMWH, factor Xa inhibitors reduced VTE (OR: 0.55, 95% CI: 0.44–0.68, high certainty), while pentasaccharide (OR: 0.61, 95% CI: 0.36–1.02, moderate certainty) probably reduced VTE, and the factor IIa inhibitor dabigatran (OR: 0.75, 95% CI: 0.40–1.42) may reduce VTE. On the other hand, compared with LMWH, UFH (OR: 1.31, 95% CI: 0.91–1.89) probably increases VTE (moderate certainty), and warfarin (OR: 1.75, 95% CI: 1.25–2.46), aspirin (OR: 1.91, 95% CI: 1.22–2.99), placebo (OR: 2.35, 95% CI: 1.71–3.24), and usual care without thromboprophylaxis (OR: 3.30, 95% CI: 2.18–4.98) increased VTE (high certainty). ►**Fig. 2** presents the network geometry and ►**Fig. 3** presents the treatment effect of each intervention. ►**Supplementary Figs. S1–S3** represent the direct effect estimates on venous thromboembolism, major bleeding and mortality respectively, in the randomized control trials. ►**Supplementary Fig. S4** presents the network funnel plot and ranking of each intervention based on *p*-scores. ►**Supplementary Table S8** summarizes the GRADE ratings for each comparison.

Based on the sensitivity analysis (►**Supplementary Table S9**), excluding studies rated as high risk of bias, combining both placebo and control arms under a common node ("no intervention"), and excluding studies published before 2000 did not substantially change the pooled estimates, or conclusions. When separating NOACs into individual medications as separate nodes, we found that compared with LMWH, rivaroxaban (OR: 0.63, 95% CI: 0.47–0.86), edoxaban (OR: 0.42, 95% CI: 0.25–0.68), and apixaban (OR: 0.52, 95% CI: 0.34–0.79) reduced the odds of VTE (all high certainty); while this was still reduced for dabigatran, this was based on low certainty evidence (OR: 0.75, 95% CI: 0.39–1.43). When stratifying aspirin based on dose, compared with LMWH, high-dose aspirin increased VTE (OR: 2.62, 95% CI: 1.31–5.23, high certainty) while low-dose aspirin probably increased VTE (OR: 1.52, 95% CI: 0.85–2.74, moderate certainty). When stratifying studies by the type of operation (hip vs. knee replacement), we did not find any significant interaction effects. Finally, subgroup analysis of 51 studies which used dose-adherent medications did not substantially change the pooled estimates or conclusions. ►**Supplementary Table S9** summarizes the results of the sensitivity and subgroup analyses.

Of 55,462 patients, 586 (1.1%) had a major bleeding event. Compared with LMWH, warfarin (OR: 0.51, 95% CI: 0.33–0.79, moderate certainty) probably decreases major bleeding and placebo (OR: 0.78, 95% CI: 0.45–1.32, low certainty) may reduce bleeding, while it is uncertain if usual care without thromboprophylaxis (OR: 0.66, 95% CI: 0.21–2.15, very low certainty) and aspirin (OR: 0.88, 95% CI: 0.47–1.63, very low certainty) has an effect on major bleeding. On the other hand, again compared with LMWH, pentasaccharide (OR: 1.54, 95% CI: 1.08–2.21, moderate certainty), UFH (OR: 1.60, 95% CI: 0.89–2.86, low certainty), and factor Xa inhibitors (OR: 1.06, 95% CI: 0.81–1.39, low certainty) may increase major bleeding, and it is uncertain if factor IIa inhibitor (OR: 1.53, 95% CI: 0.80–2.91, very low certainty) has an effect on major bleeding.

In total, 88 out of 50,768 (0.17%) patients died. Compared with LMWH, it is uncertain if any of the interventions had an important impact on mortality; these include factor IIa

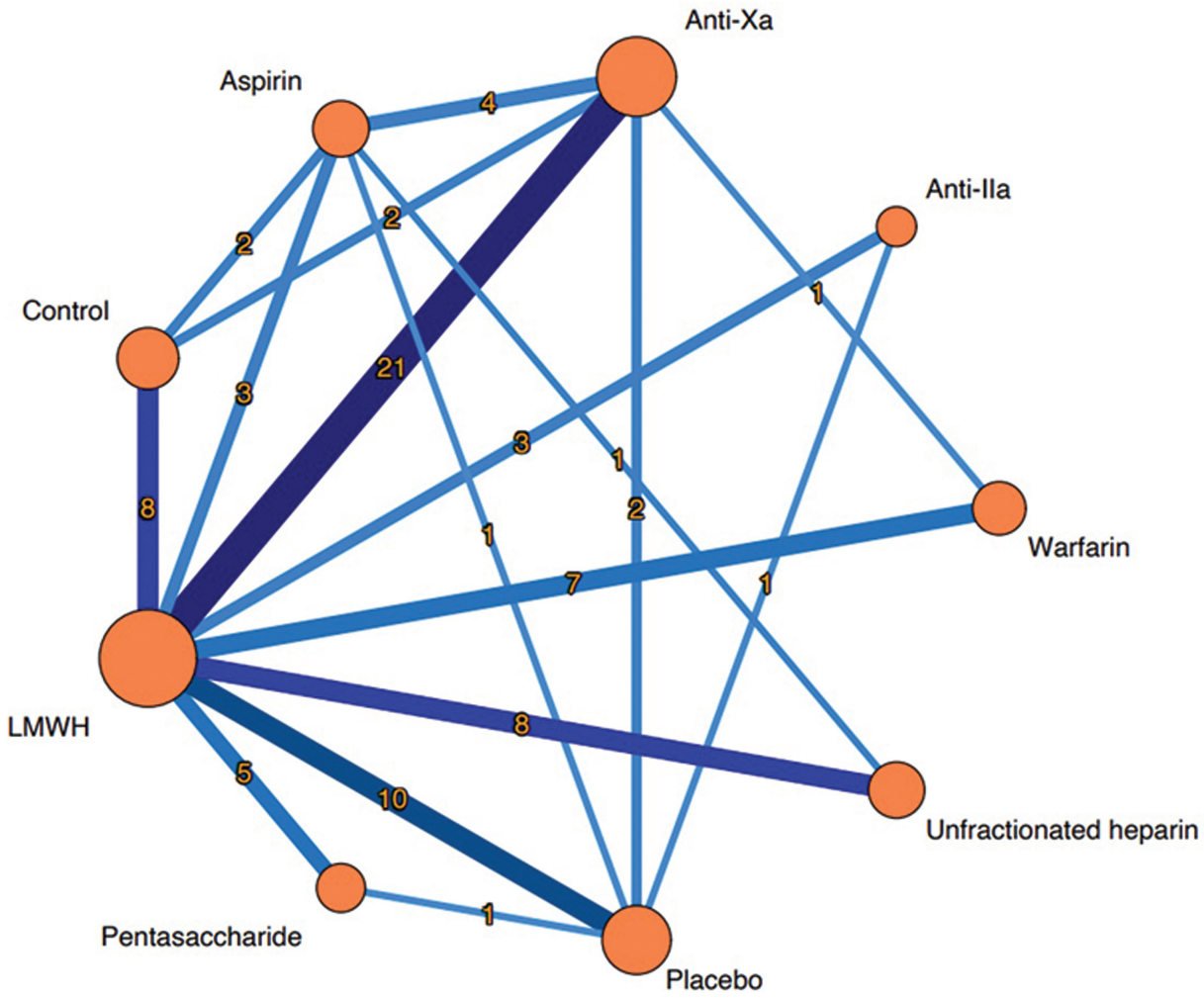

Fig. 2 Geometry of the network meta-analysis for venous thromboembolism. The size of each circle (or node) represents the number of studies reporting on each intervention, and the thickness and depth of color of each line (or edge) represents the number of studies comparing between both interventions.

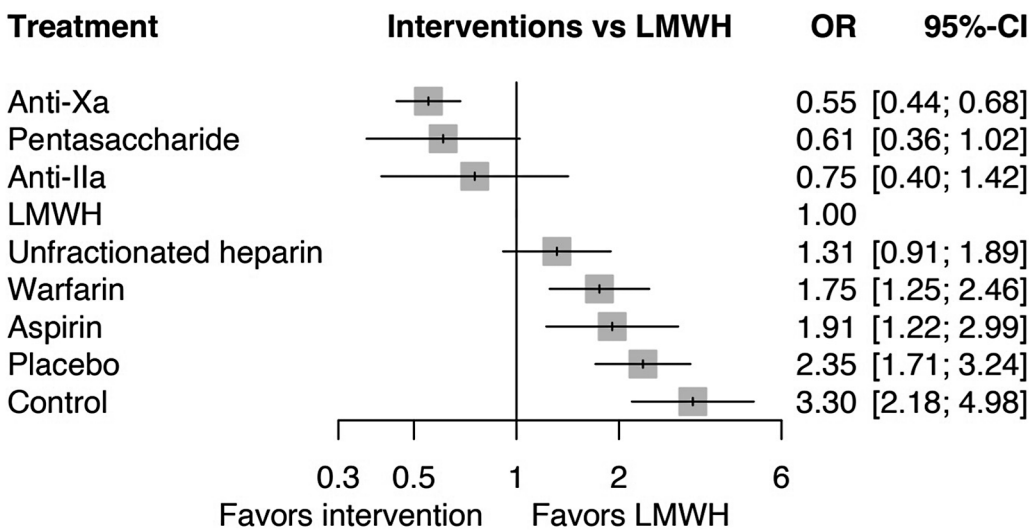

Fig. 3 Forest plot representing the treatment effect of each intervention compared with low-molecular-weight heparin (the reference group) for venous thromboembolism.

inhibitor (OR: 0.54, 95% CI: 0.09–3.41), placebo (OR: 0.88, 95% CI: 0.23–3.33), factor Xa inhibitors (OR: 1.02, 95% CI: 0.61–1.72), aspirin (OR: 1.07, 95% CI: 0.33–3.45), usual care without thromboprophylaxis (OR: 1.00, 95% CI: 0.06–17.41), warfarin (OR: 1.36, 95% CI: 0.63–2.93), pentasaccharide (OR: 1.31, 95% CI: 0.32–5.37), and UFH (OR: 2.04, 95% CI: 0.54–7.67, all very low certainty). ►**Supplementary Figs. S5** and **S6** present the network geometry, treatment effects of each intervention, funnel plot, and ranking of each intervention for major bleeding and death respectively, while ►**Supplementary Tables S10** and **S11** summarize the GRADE ratings for major bleeding and death, respectively.

We conducted a TSA for pairwise comparisons of interventions for outcomes of interest (►**Supplementary Tables S12–S14**). Notably, in the comparison of factor Xa inhibitors versus LMWH in preventing VTE, the required information size is attained, and the cumulative Z-curve crosses the boundary for benefit in favor of factor Xa inhibitors. This further supports the conclusion that factor Xa inhibitors are superior to LMWH in preventing VTE. The comparison of aspirin, warfarin, placebo, and control versus LMWH all attained the required information size, and the cumulative Z-curve crosses the boundary for benefit in favor of LMWH.

Discussion

In this network meta-analysis of 70 RCTs including 55,841 patients, we found, compared with LMWH, that factor Xa inhibitors reduced the odds of VTE without increasing the odds of bleeding or death. Of note, factor IIa inhibitor did not reduce VTE, and warfarin and aspirin increased the odds of VTE, in comparison to LMWH. These results were consistent across several sensitivity and subgroup analyses, which increases the certainty in the findings.

Existing guidelines support pharmacological VTE prophylaxis in elective THA or TKA,[24] though the specific prophylactic strategy varies. Some guidelines recommend LMWH over factor Xa inhibitors,[23] and others recommend NOACs or specifically rivaroxaban.[26] Yet, factor Xa inhibitors, and specifically rivaroxaban, may be associated with increased risks of major bleeding[117–120] when compared with LMWH or apixaban based on a previous network meta-analysis of 19 RCTs.[117] In the current network meta-analysis, factor Xa inhibitors as a group, and individually, were associated with reduced VTE events, but not factor IIa inhibitor. We also did not find an increase in major bleeding when comparing LMWH and factor Xa inhibitors, as well as most other medications. While pentasaccharides are an exception, this is consistent with prior studies.[121] These results support the use of factor Xa inhibitors in reducing VTE post-arthroplasty. In addition, whereas LMWH requires parenteral administration, factor Xa inhibitors can be administered orally, which may be more comfortable for patients and facilitate adherence to outpatient extended thromboprophylaxis.[122]

The role of aspirin as pharmacological thromboprophylaxis remains controversial: while it is recommended for VTE prophylaxis,[22,23] it is unclear if it is preferred over other medications. Although some guidelines recommend low-dose aspirin as the ideal agent for VTE prophylaxis based on a network meta-analysis of RCTs and observational studies,[26] other guidelines and meta-analyses based on small, low-quality studies found based on low certainty no differences between aspirin and LMWH[123] or other anticoagulants.[22,30] More recent studies suggest that low-dose aspirin was inferior to LMWH, and was associated with a higher risk of VTE than previously reported.[102,116,124,125] In the current network meta-analysis, we found that studies using aspirin as a whole reported higher rates of VTE relative to LMWH. As such, the choice of aspirin as a viable alternative to LMWH should be revisited.

There are several strengths to our study. We combined a network meta-analysis with a TSA, which helped inform the current state of the evidence and literature. In the context of the above, it is unlikely that further trials are required to investigate the efficacy of factor Xa inhibitors as venous thromboprophylaxis in joint arthroplasty. In addition, we conducted subgroup analysis focusing on specific dosing in a real-world context, which aids in transitivity (where indirect estimates accurately mirror an unobserved direct estimate, requiring potential effect modifiers to be similar between studies). The inclusion of other interventions such as pentasaccharide and warfarin increased the sample size and hence, the precision of our analysis. Our analysis is based on a prespecified protocol, and a robust librarian-verified search strategy with comprehensive inclusion criteria. Furthermore, we included unpublished data,[48] which reduces the risk of publication bias. Compared with previous studies,[30,117,123] we included more RCTs and investigated a broader range of medications, which also increases the sample size and hence, precision. We applied the GRADE to communicate findings transparently and efficiently. We adopted more comprehensive and consistent definitions of bleeding,[126] which helps overcome heterogeneity. We stratified the odds of VTE based on individual types of surgery, which is critical in informing future practice for orthopedic surgeons.

However, there are also limitations to this study. First, despite optimizing our inclusion criteria and conducting additional analyses, we detected statistical inconsistency, which may be due to several factors, including changing clinical practices over time, patient demographics and inherent differences in VTE rates across ethnicities,[6] and differences in follow-up durations between studies. Within our study, possible contributors to intransitivity include immobilization,[127] type of anesthesia,[128,129] and co-interventions including mechanical prophylaxis such as graduated compression stockings and intermittent pneumatic compression[130] devices. In addition, in view of the transitivity assumption and lack of randomized data, we could not include studies reporting on hybrid regimens for venous thromboprophylaxis. It is difficult to quantify these interaction effects in the frequentist framework for network meta-analyses, and current software do not allow for covariate adjustment. This is compounded by the fact that these sources of variability were poorly reported and as such, their effect remains unknown. In addition, as a result of applying stricter inclusion criteria to optimize consistency, we reduced the sample size and precision of our analysis. As

such, certain estimates, and the analysis stratified based on the type of surgery, may not be informative due to lack of power rather than a lack of actual differences. There is also a possibility of double counting patients who had both DVT and PE, though this is likely limited to a small subset of patients.[131,132] We were unable to analyze the cost effectiveness of each regimen in view of a paucity of data, though this would also be important to patients and other stakeholders involved. There may be important heterogeneity in the bleeding data as the definitions of major bleeding as a primary safety outcome vary considerably among the RCTs. Studies that excluded surgical-site bleeding from their definition of major bleeding reported major bleeding rates approximately 10 times lower than those studies that included it. In certain RCTs assessing rivaroxaban,[74,97,98,115,116] the definition of major bleeding did not encompass surgical-site bleeding. The majority of trials involving rivaroxaban and apixaban used the hemoglobin level on the first postoperative day as a baseline (to avoid the confounder of intraoperative blood loss) to identify significant drops in hemoglobin as indicative of major bleeding. Moreover, reporting of bleeding was also inconsistent. Some trials reported on the volume of blood transfusion required rather than the number of patients who had a bleeding event; this could not be incorporated into the meta-analysis. Finally, our study population is also not representative of certain patient groups, such as patients with renal impairment or inherited bleeding disorders.

Conclusion

This frequentist network meta-analysis found that factor Xa inhibitors decrease VTE compared with LMWH and aspirin when used as VTE prophylaxis after elective THA or TKA, without increasing the risk of bleeding or mortality. On the other hand, several agents (aspirin, warfarin) increased the odds of VTE compared with LMWH.

Conflicts of Interest

R.R.L. receives research support from the Clinician Scientist Development Unit, Yong Loo Lin School of Medicine, Singapore. All other authors declare no competing interests.

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