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Acetylsalicylic Acid for Venous Thromboembolism Prophylaxis in Total Hip or Knee Replacement: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Development
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
ASA	Acetylsalicylic acid
ASH	American Society of Hematology
BMI	Body mass index
DVT	Deep vein thrombosis
ESA	European Society of Anesthesiology
LMWH	Low molecular weight heparin
NICE	National Institute for Health and Care Excellence
PE	Pulmonary embolism
RCT	Randomized controlled trial
SR	Systematic review
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VTE	Venous thromboembolism

Context and Policy Issues

Patients undergoing orthopedic surgery, particularly total hip or knee replacement, also referred as total hip arthroplasty (THA) or total knee arthroplasty (TKA), are at high risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] Approximately 59,000 THA and 70,000 TKA were performed in Canada in 2017 and 2018.[2] Without pharmacologic prophylaxis, the rate of VTE, both asymptomatic and symptomatic, could be as high as 84% for patients undergoing TKA and THA.[3] The rate of symptomatic VTE following THA or TKA in patients receiving pharmacologic prophylaxis has been reported to be at 0.5 to 1% during in-hospital stay,[4] and potentially increased up to 2% during 90 days after surgery.[5]

Current available chemoprophylactic agents include low molecular weight heparin (LMWH; enoxaparin, dalteparin), vitamin K antagonists (warfarin), direct Factor Xa inhibitors (rivaroxaban, apixaban), direct thrombin inhibitor (dabigatran) and aspirin (also known as acetylsalicylic acid, ASA).[6] These agents differ among each other in terms of mechanism of action, potency, efficacy and safety.[6]

Unlike the other anticoagulants, ASA does not affect any step in the coagulation cascade, rather it irreversibly inhibits cyclooxygenase-1, an enzyme involved in platelet aggregation.[6] ASA has been recently found to be involved in several mechanisms of venous thrombosis in addition to its anti-platelet aggregation property,[7] suggesting its involvement in VTE prophylaxis. Interest in ASA as a means of VTE prophylaxis has recently grown, and recent literature suggests that ASA could be a viable option for VTE prophylaxis following THA or

TKA, due to its potentially favorable efficacy and safety profile.[6] A recent 2017 CADTH report[8] found mixed evidence on the clinical effectiveness of ASA compared with LMWH and Factor Xa inhibitors.

The aim of this report is to review the evidence regarding the clinical effectiveness and evidence-based guidelines regarding the use of ASA for VTE prophylaxis in patients undergoing THA or TKA. The term aspirin is used interchangeably with ASA throughout this review, particularly in the Summary of Evidence section, to be consistent with the terminology used in all included studies.

Research Questions

1. What is the clinical effectiveness of acetylsalicylic acid for venous thromboembolism prophylaxis in individuals undergoing total hip or knee replacement?
2. What are the evidence-based guidelines regarding the use of acetylsalicylic acid for venous thromboembolism prophylaxis in individuals undergoing total hip or knee replacement?

Key Findings

This review included five systematic reviews of randomized controlled trials, 15 non-randomized studies (i.e., 14 retrospective and one prospective in design) regarding the clinical effectiveness and safety of ASA for venous thromboembolism prophylaxis in patients undergoing total hip or knee arthroplasty, and three evidence-based guidelines regarding the use of aspirin in this population.

In terms of effectiveness and safety profile, the use of ASA for venous thromboembolism prophylaxis after total hip or knee arthroplasty was generally not associated with significant differences compared to alternative anticoagulants including low molecular weight heparins (enoxaparin, dalteparin), Factor Xa inhibitors (rivaroxaban, apixaban), direct thrombin inhibitor (dabigatran), warfarin, or another anticoagulants. All three included guidelines recommend the use of aspirin for venous thromboembolism prophylaxis in patients undergoing total hip or knee arthroplasty based on low quality evidence. Due to significant limitations of the evidence, interpretations of the findings should be taken with cautions.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All via Ovid, Embase via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were acetylsalicylic acid and venous thromboembolism prophylaxis in individuals undergoing total hip or knee replacement. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and July 22, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals undergoing total hip or knee replacement
Intervention	Acetylsalicylic acid (i.e., aspirin; alone or as an adjunct to other anticoagulant therapies)
Comparator	Q1: Other anticoagulant drugs (e.g., low-molecular-weight heparin, Factor Xa inhibitors); physical methods for venous thromboembolism prophylaxis (e.g., mobilization, graduated compression stockings, intermittent pneumatic compression device); no treatment; placebo Q2: No comparator required
Outcomes	Q1: Clinical effectiveness (e.g., incidence of venous thromboembolism, rate of readmission, safety [e.g., unexpected bleeding, rates of adverse events]) Q2: Recommendations regarding best practices (e.g., guidance regarding appropriate patient populations and patient monitoring, treatment protocols, and dosing regimens)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, and evidence-based guidelines

RICE = rest, ice, compression, and elevation.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 they were duplicate publications, or were published prior to 2017. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Studies that had been included in the previous 2017 CADTH report,[8] were also excluded. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) checklist.[9] The critical appraisal checklist of Downs and Black was used to assess the quality of the included non-randomized studies.[10] The quality of the included evidence-based guideline was assessed using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[11] Summary scores were not calculated for the included studies; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 156 citations were identified in the literature search. Following screening of titles and abstracts, 103 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of the 55 potentially relevant articles, 32 publications were excluded for various reasons, while 23 publications met the inclusion

criteria and were included in this report. These comprised five SRs, 15 primary studies, and three guidelines. Appendix 1 presents the PRISMA flowchart[12] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included SRs,[13-17] (Table 2) primary studies[18-32] (Table 3) and the ASH (American Society of Hematology),[33] NICE (National Institute for Health and Care Excellence)[34] and the ESA VTE (European Society of Anesthesiology Venous Thromboembolism)[35] guidelines (Table 4) are presented in Appendix 2.

Study Design

Four included SRs[13,14,16,17] were comprised of only RCTs, and one SR[15] included four RCTs and one retrospective cohort study. The number of included studies in the SRs ranged from four to 13. All included SRs performed literature searches from multiple databases from database inception to January 1, 2020,[13] September 19, 2019,[14] August 2018,[15,16] and February 21, 2018.[17] Four SRs[13-15,17] used the Cochrane risk of bias instrument, and one SR[16] used the Jadad scoring tool to assess the methodological quality of the included studies. Four SRs[13-16] used random-effects or fixed-effects models meta-analysis to obtained the summary estimates of direct comparisons, and one SR[17] used random-effects network meta-analysis to combine direct and indirect evidence.

Of 15 included primary studies, 14[18-30,32] were of retrospective design, and one[31] was of prospective design. Nine[18,21-23,25-27,30,32] were retrospective chart review studies using data from multi-institutional databases, or databases from National Registry or from healthcare insurance. Three[19,20,24] were retrospective cohort studies, two[28,29] were retrospective case-matched studies, and one[31] was a six-year prospective cohort study from single institutions. Nine studies[18,19,22,23,25,27,28,30,32] adjusted for potential confounding factors in their analyses of primary endpoints. Six studies[20,21,24,26,29,31] did not conduct any adjustment for covariates in their analyses. Two studies[19,23] used a non-inferiority analysis to compare the effectiveness of aspirin with its comparators.

All three included guidelines[33-35] were developed by multidisciplinary guideline committees, which consisted of healthcare professionals who were directly or indirectly involved in the care of patients undergoing major surgery, including total joint replacement surgery, and methodologists with expertise in evidence appraisal and guideline development. The guidelines used systematic methods to search for, select, and synthesize evidence. The recommendations were evidence-based, and consensus based. The ASH guideline[33] graded its recommendations based on the certainty of evidence ranging from high to very low. The ESA VTE guideline[35] graded its recommendations (strong or weak) based on the level of evidence (from high to very low). The NICE guideline[34] did not provide grading of its recommendations.

Country of Origin

The included SRs were conducted by authors from Australia,[13,15,17] UK[14] and USA.[16]

The included primay studies were conducted by authors from UK,[18,24] Ireland,[19] USA,[20-23,25-28,30-32] and Thailand.[29]

The included guidelines were conducted by authors from Canada and USA,[33] UK[34] and France.[35]

Patient Population

All SRs[13-17] included studies with adult patients who underwent THA or TKA. The mean age ranged from 63 to 71 years. The proportion of males ranged from 24% to 44%. Total number of patients ranged from 1,507 to 20,115.

The primary studies included patients who underwent THA or TKA,[18-20,22,24-28,32] THA only,[21] or TKA only.[23,29-31] The mean age ranged from 63.6 years to 70.7 years. The proportion of males ranged from 12.3% to 44.7%.

The target populations in the ASH[33] and the ESA VTE[35] guidelines are patients undergoing major surgery included THA and TKA. The target populations in the NICE guideline[34] are adult and young people aged16 and over admitted to hospital or attending hospital for day procedures. The intended users of all included guidelines[33-35] are healthcare professionals.

Interventions and Comparators

Two SRs[13,17] included RCTs comparing aspirin with a LMWH (i.e., enoxaparin). The dose of aspirin ranged from 100 mg once daily to 325 mg twice daily, and the dose of enoxaparin ranged from 40 mg once daily to 30 mg twice daily.

One SR[15] included four RCTs and one retrospective cohort study comparing aspirin with a Factor Xa inhibitor, rivaroxaban. The dose of aspirin ranged from 81 mg once daily to 325 mg twice daily, and the dose of rivaroxaban was 10 mg once daily.

Two SRs[14,16] included RCTs comparing aspirin with another anticoagulant. The dose of aspirin ranged from 81 mg once daily to 650 mg twice daily. The doses of another anticoagulant reported in one SR[14] were: rivaroxaban (10 mg once daily), LMWH (4000 unit once daily), dalteparin (5000 unit once daily), enoxaparin (40 mg once daily), low molecular weight dextran (500 mL once daily), warfarin (7.5 mg or 10 g initially then dose titrated based on prothrombin time).

Treatment duration was reported in three SRs,[13,15,16] ranging from nine days to 35 days. Four SRs[14-17] reported follow-up periods, ranging from nine days to one year.

Two included primary studies[19,27] compared aspirin with a LMWH (i.e., enoxaparin). The dose of aspirin ranged from 81 mg once daily to 325 g twice daily, and the dose of enoxaparin was 40 mg once daily. Treatment duration of aspirin varied from four to six weeks, while enoxaparin was administered only until discharge[19] or were given for four to six weeks after surgery.[27]

Four included primary studies[18,19,29,31] compared aspirin with a Factor Xa inhibitor (i.e., rivaroxaban). Three primary studies[19,29,31] reported aspirin doses ranging from 150 mg once daily to 325 mg once daily. Two primary studies[19,29] reported rivaroxaban dose which was 10 mg daily. Three primary studies[19,29,31] reported treatment duration. The treatment duration of aspirin varied from 14 days to 90 days, while the treatment duration of rivaroxaban varied from 14 days to 35 days.

Two included primary studies[18,24] compared aspirin with a direct thrombin inhibitor (i.e., dabigatran). Treatment dose and duration were reported in one study.[24] Aspirin was administered at 150 mg once daily for six weeks after both THA and TKA, while dabigatran was given at 220 mg once daily for 28 days after THA, or 10 days after TKA.

Three included primary studies[20,27,30] compared aspirin with warfarin. The dose of aspirin was either 81 mg twice daily or 325 mg twice daily. The dose of warfarin was titrated against an international normalized ratio target of between 1.5 to 2.5. Treatment duration was four weeks in both treatment arms and in all studies.

Six studies[21-23,25,26,28] compared aspirin with non-aspirin strategies (i.e., another anticoagulant). All studies did not report treatment duration and four studies did not report the dose of aspirin or anticoagulant drugs. Doses of aspirin and another anticoagulant were reported in two studies.[22,28] One study[22] compared aspirin (80 to 325 mg) with another anticoagulant, such as unfractionated heparin (5000 to 7500 units), LMWH (i.e., enoxaparin [20 to 40 mg], dalteparin [2500 to 5000 units]), fondaparinux (2.5 mg), warfarin (any dose), and Factor Xa inhibitors (i.e., apixaban [2.5 mg], rivaroxaban [10 mg]). One study[28] compared aspirin (81 mg twice daily to 325 twice daily) with another anticoagulant, such as apixaban (2.5 mg daily), dabigatran (220 mg daily), or rivaroxaban (10 mg daily).

Follow-up periods of all included primary studies ranged from 48 hours to one year.

The interventions and practices considered in the evidence-based guidelines were different modalities, including pharmacological antithrombotic prophylaxis and mechanical prophylaxis, for prevention of VTE in the ASH and NICE guidelines,[33,34] or specifically aspirin in the ESA VTE guideline.[35]

Outcomes

Among the included SRs[13-17] and primary studies,[18-32] the clinical effectiveness outcomes included VTE (DVT and/or PE), DVT only, and PE only. The safety outcomes included death, bleeding, wound infections/complications, and readmission.

All three included guidelines[33-35] considered clinical, economic and safety outcomes of VTE prophylaxis options including aspirin for the prevention of VTE in patients who undergo major surgery including orthopedic surgery such as TKA and THA.

Summary of Critical Appraisal

The detailed quality assessments of the included SRs,[13-17] (Table 5) primary studies,[18-32] (Table 6 and Table 7) and guidelines[33-35] (Table 8) are presented in Appendix 3.

All included SRs[13-17] were explicit in terms of research questions and inclusion criteria for the review, selection of study design for inclusion, comprehensive literature search strategy, study selection and data extraction, which were performed in duplicate. Three SRs[13,14,17] had a protocol published prior to the conduct of the review. One SR[17] reported the sources of funding of the studies included in its review. None of the SRs provided a list of excluded studies. All SRs described the included studies in adequate detail, used appropriate techniques to assess the risk of bias of the included studies, used appropriate methods to combine the results, accounted for the risk of bias in individual studies when interpreting or discussing the results, and reported conflict of interest as well as the source of funding received for conducting the review. Overall, all included SRs were of acceptable methodological quality.

All included primary studies, except one,[21] were explicit in reporting (i.e., clearly described the objective of the study, the main outcomes, the characteristics of the participants, the interventions, distributions of confounders in each group, and the main findings of the study). Five studies[21,24,26,28,29] did not provide estimates of the random variability (e.g.,

standard deviation or 95% confidence interval) in the data of the main outcome. Actual probability values were reported in all studies for main outcomes, except one.[31] As most of the included studies were database reviews or chart reviews, it was not applicable to determine if the participants were representative of the entire population from which they were recruited. However, the treatment settings were representative of the treatment received by most of the patients. The intervention and comparator groups in all included studies had the same follow-up. Appropriate statistical tests were used to assess the main outcomes, which were accurately measured. Of the included studies, two retrospective cohort studies,[20,24] one retrospective case-matched study[29] and one prospective cohort study[31] had patients in the intervention and comparator groups recruited from different populations and at different periods of time. Of fifteen studies, six[20,21,24,26,29,31] did not identify or conduct any adjustment for potential confounders in the analyses from which the main findings were drawn. The findings in those studies were therefore considered as crude and less reliable. Overall, the majority of the included studies were large retrospective database reviews with acceptable methodological quality.

All included guidelines[33-35] were explicit in terms of scope and purpose (i.e., objectives, health questions and populations), and had clear presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups; however, it was unclear in one guideline[35] if the views and preferences of the target populations were sought. For rigour of development, all guidelines explicitly reported details of systematic searches for evidence, criteria for selecting evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, health benefits, side effects, and risks in formulating the recommendations, and were peer-reviewed prior to publication. All included guidelines provided a procedure for updating. For applicability, the guidelines were explicit in terms of facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource (cost) implications, and monitoring and or auditing criteria. For editorial independence, the guidelines reported that the funding bodies had no influence on the content of the guidelines. The competing interests of the guideline development group members were reported. Overall, all three included guidelines were of high methodological quality.

Summary of Findings

The main findings and authors' conclusions of the SRs,[13-17] (Table 9), primary studies[18-32] (Table 10), and guidelines[33,34 35] (Table 11) are presented in Appendix 4. The presentation of the findings are ordered by comparisons followed by outcomes. High-level summaries of findings in SRs and primary studies are shown in Table 12 and Table 13, respectively.

Aspirin versus LMWH

Clinical Effectiveness

VTE

The meta-analysis of data from four RCTs included in one SR[13] showed that there was no significant difference in the overall rate of VTE when comparing aspirin with enoxaparin for VTE prophylaxis in THA or TKA. The included trials had significant risk of bias, and the quality of evidence was very low as assessed by the authors.

The meta-analysis of data from five RCTs included in another SR[14] showed that there was no significant difference in the risk of VTE between patients receiving aspirin and those receiving LMWH (i.e., enoxaparin, dalteparin) after THA or TKA. Most included RCTs had high risk of bias as assessed by the authors. The most common biases were blinding and allocation concealment.

One retrospective cohort study,[19] from a single institution, comparing an extended aspirin regimen (N = 3,460) with inpatient enoxaparin regimen (N = 961) during six months after THA or TKA, found no significant difference in total VTE rates between the two treatment groups, after adjustment for covariates. Non-inferiority analysis suggested equivalence in VTE risk between the two regimens.

One retrospective multi-institutional chart review[27] using data from three institutions, found that patients receiving aspirin (N = 13,610) was associated with significantly lower risk of VTE in both VTE standard-risk and VTE high-risk groups compared to those receiving enoxaparine (N = 17,554) during 90 days after THA or TKA. Both univariate and multivariate analyses (adjustment for covariates) produced the same results.

DVT

Two SRs, one[13] conducting meta-analysis of data from four RCTs, and one[17] conducting network meta-analysis of data from nine RCTs, incorporating direct and indirect evidence, found that there was no significant difference in total DVT rates between aspirin and enoxaparin after THA or TKA. In both SRs, the quality of evidence was graded as very low. Aspirin was found to be associated with a higher Netrank *p*-score generated by the network meta-analysis as compared with enoxaparin (0.94 versus 0.55), suggesting that aspirin treatment was more reliable, and greater consistency and certainty for total DVT.[17]

The meta-analysis of data from five RCTs included in one SR[14] showed that there was no significant difference in the risk of DVT between patients receiving aspirin and those receiving LMWH (i.e., enoxaparin, dalteparin) during 90 days after THA and TKA.

PE

Two SRs, one[13] conducting meta-analysis of data from three RCTs, and one[17] conducting network meta-analysis of data from two RCTs, found that there was no significant difference in total PE rates between aspirin and enoxaparin after THA or TKA. In both SRs, the quality of evidence was graded as very low. Aspirin was found to be associated with a higher Netrank *p*-score compared with enoxaparin (0.68 versus 0.44).[17]

The meta-analysis of data from five RCTs included in one SR[14] showed that there was no significant difference in the risk of PE between patients receiving aspirin and those receiving LMWH (i.e., enoxaparin, dalteparin) after THA or TKA.

Safety

Bleeding

Two SRs showed no significant differences in the rates of major bleeding[13,17] or minor bleeding[13] between aspirin and enoxaparin groups after THA or TKA. The quality of evidence was graded as moderate to very low.[13,17] There was no differences in Netrank *p*-scores between aspirin and enoxaparin (0.51 versus 0.50).[17]

Wound infections/complications

The network meta-analysis of data from two RCTs conducted by one SR[17] found no significant difference in rates wound complications between aspirin and enoxaparin in patients undergone THA or TKA. Aspirin had higher Netrank *p*-score compared to enoxaparin (0.79 vs 0.46). The quality of evidence was considered to be very low, as assessed by the authors.

One retrospective multi-institutional chart review[27] using data from three institutions found that patients receiving aspirin (N = 13,610) was associated with significantly lower periprosthetic joint infections rate compared with those receiving enoxaparin (N = 17,554) in both VTE standard-risk and VTE high-risk groups during 90 days after THA or TKA.

Overall, three SRs,[13,14,17] one retrospective cohort study[19] and one retrospective chart review study[27] provided evidence for the clinical effectiveness and safety of aspirin compared with LMWH (enoxaparin, dalteparin). For clinical effectiveness, the use aspirin as VTE prophylaxis after THA or TKA was not associated with any significant difference in the rate of VTE, including DVT and PE, as compared with LMWH. For safety, there were no significant differences in the rates of bleeding and wound infections or wound complications between the treatment modalities. In the retrospective chart review study,[27] the rates of VTE and periprosthetic joint infections in the aspirin group were significantly lower compared to that in the enoxaparin group.

Aspirin versus Factor Xa Inhibitors

Clinical Effectiveness

VTE

The meta-analysis of data from three RCTs included in one SR[14] showed that there was no significant difference in the risk of VTE between patients receiving aspirin and those receiving rivaroxaban after THA or TKA. Most included RCTs had high risk of bias as assessed by the authors.

The meta-analysis of data from four RCTs included in one SR[15] showed that there was no significant difference in VTE rates between aspirin and rivaroxaban after THA or TKA. The quality of the included RCTs assessed by the authors was low or had an unclear risk of bias.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that there was significantly higher risk of VTE associated with the use of aspirin (N = 44,135) compared with rivaroxaban (N = 44,135) during 90 days after both THA and TKA. Propensity score matching was used to control for potential patient and surgical confounding factors.

One retrospective cohort study from a single institution,[19] comparing an extended aspirin regimen (N = 3,460) with modified rivaroxaban regimen (N = 1,212) during six months after THA or TKA, found no significant difference in total VTE rates between the two treatment groups, after adjustment for covariates. Non-inferiority analysis suggested equivalence in VTE risk between the two regimens.

DVT

The meta-analysis of data from three RCTs included in one SR[14] showed that there was no significant difference in the risk of DVT between patients receiving aspirin and those receiving rivaroxaban after THA or TKA.

The meta-analysis of data from four RCTs included in one SR[15] showed that there was no significant difference in DVT rates between aspirin and rivaroxaban groups after THA or TKA.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that there was no significant difference in the rates of DVT between aspirin (N = 44,135) and rivaroxaban (N = 44,135) groups during 90 days after both THA and TKA.

One retrospective case-matched study[29] using data from one institution found no DVT events in both aspirin (N = 79) and rivaroxaban (N = 76) groups during 48 hours after TKA.

A six-year prospective cohort study[31] from a single institution found that there was no significant difference in the rates of DVT between combination of aspirin and fish oil (N = 300) and rivaroxaban (N = 250) groups after TKA.

PE

The meta-analysis of data from two RCTs included in one SR[15] showed that there was no significant difference in PE rates between aspirin and rivaroxaban groups after THA or TKA.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that there was significantly higher risk of PE associated with the use of aspirin (N = 44,135) compared with rivaroxaban (N = 44,135) during 90 days after both THA and TKA.

One retrospective case-matched study,[29] using data from one institution, found no PE events in both aspirin and rivaroxaban groups during 48 hours after TKA.

A six-year prospective cohort study,[31] from a single institution, found no PE events in both aspirin (N = 300) and rivaroxaban (N = 250) groups during 90 days after TKA.

Safety

Death

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man found no difference in the risk of death in patients receiving aspirin (N = 44,135) compared with those receiving rivaroxaban (N = 44,135) during 90 days after both THA and TKA.

Bleeding

The meta-analysis of data from two RCTs included in one SR[15] showed that there was no significant difference in both major and any bleeding rates between aspirin and rivaroxaban groups after THA or TKA.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no difference in the risk of major

bleeding in patients receiving aspirin (N = 44,135) compared with those receiving rivaroxaban (N = 44,135) during 90 days after both THA and TKA.

One retrospective case-matched study,[29] using data from one institution, found no bleeding-related complications in both aspirin (N = 79) and rivaroxaban (N = 76) groups during 48 hours after TKA.

A six-year prospective cohort study[31] from a single institution, found that combination of aspirin and fish oil was associated with significantly lower rate of bleeding compared to rivaroxaban during 90 days after TKA.

Wound infections/complications

The meta-analysis of data from three RCTs included in one SR[15] found that there was no significant difference in the rate of wound complications between aspirin and rivaroxaban groups after THA or TKA.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no significant difference in wound disruption in patients receiving aspirin (N = 44,135) compared with those receiving rivaroxaban (N = 44,135) during 90 days after both THA and TKA.

Readmission

The meta-analysis of data from two RCTs included in one SR[15] found that there was no significant difference in readmission rate between aspirin and rivaroxaban groups after THA or TKA.

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that there was significantly higher risk of readmission in patients receiving aspirin (N = 44,135) compared to those receiving rivaroxaban (N = 44,135) during 90 days after both THA and TKA.

Overall, two SRs[14,15] and four retrospective studies, including one retrospective chart review study,[18] one retrospective cohort study,[19] one retrospective case-matched study[29] and one prospective cohort study[31] provided mixed evidence for the clinical effectiveness and safety of aspirin compared with Factor Xa inhibitors (rivaroxaban or apixaban) as VTE chemoprophylaxis in patients undergoing THA or TKA. For clinical effectiveness, the results of two SRs[14,15] and three retrospective studies[19,29,31] showed no significant difference between aspirin and Factor Xa inhibitors in VTE including DVT and PE. For safety, the results from those studies also showed no significant differences in the rates of bleeding, wound complications, and hospital readmission. However, one retrospective chat review study[18] found that, compared with rivaroxaban or apixaban, aspirin was associated with significantly higher risk of VTE, PE, and readmission, but with non-significant difference in DVT, mortality, bleeding, or wound disruption.

Aspirin versus Direct Thrombin Inhibitors

Clinical Effectiveness

VTE

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that there was significantly higher risk of VTE associated with the use of aspirin (N = 62,210) compared with dabigatran (N =

62,210) during 90 days after both THA and TKA. Propensity score matching was used to control for potential patient and surgical confounding factors.

One retrospective cohort study,[24] using two consecutive 6-month sets of data from one institution (one for dabigatran and one for aspirin), found that the rate of VTE in the aspirin group (N = 301) was not significantly different than that in the dabigatran group (N = 346) during 90 days after THA or TKA.

DVT

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that the use aspirin (N = 62,210) was associated with significantly higher risk of DVT compared with dabigatran (N = 62,210) after THA, but there was no significant difference in the rate of DVT between the two treatments after TKA. Follow-up was 90 days.

PE

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found that the use aspirin (N = 62,210) was associated with significantly higher risk of PE compared with dabigatran (N = 62,210) after THA, but there was no significant difference in the rate of PE between the two treatments after TKA. Follow-up was 90 days.

Safety

Death

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no significant difference in mortality between patients receiving aspirin (N = 62,210) compared with those receiving dabigatran (N = 62,210) during 90 days after both THA and TKA.

One retrospective cohort study,[24] using two consecutive 6-months data from one institution (one for dabigatran and one for aspirin), found no significant difference in the rate of mortality between aspirin (N = 301) and dabigatran (N = 346) during 90 days after THA or TKA.

Bleeding

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no significant difference in the risk of major bleeding between patients receiving aspirin (N = 62,210) compared with those receiving dabigatran (N = 62,210) during 90 days after both THA and TKA.

Wound infections/complications

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no significant difference in the risk of wound disruption between patients receiving aspirin (N = 62,210) compared with those receiving dabigatran (N = 62,210) after both during 90 days THA and TKA.

Readmission

One retrospective chart review,[18] using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man, found no significant difference in readmission

rates between patients receiving aspirin (N = 62,210) compared with those receiving dabigatran (N = 62,210) during 90 days after both THA and TKA.

One retrospective cohort study,[24] using two consecutive 6-months data from one institution (one for dabigatran and one for aspirin), found no significant difference in readmission rates between aspirin (N = 301) and dabigatran (N = 346) during 90 days after THA or TKA.

Overall, one retrospective chart review study[18] and one retrospective cohort study[24] provided mixed evidence for clinical effectiveness of aspirin compared with direct thrombin inhibitors (i.e., dabigatran) as VTE prophylaxis in patients undergoing THA or TKA. For clinical effectiveness, a retrospective chart review study[18] found that aspirin was associated with significantly higher risk of VTE after both THA and TKA. Similar results were found for DVT and PE after THA, but not TKA, where no significant differences were observed between the two treatments. A retrospective cohort study[24] did not find any significant differences between aspirin and dabigatran in terms of VTE, DVT and PE after both THA and TKA. For safety, retrospective chart review study[18] found no significant differences between two treatments in terms of mortality, bleeding, wound disruption and readmission after both THA and TKA. A retrospective cohort study[24] also found no significant differences between aspirin and dabigatran groups in the rates of death and readmission after both THA and TKA.

Aspirin versus Warfarin

Clinical Effectiveness

VTE

One retrospective cohort study,[20] comparing aspirin (N = 243) with warfarin (N = 206) in the presence of sequential compression device as VTE prophylaxis in patients underwent TKA or THA, found no significant difference in the rate of VTE between two treatment groups after 30 days of follow-up.

One retrospective chart review,[27] using data from three institutions, found that aspirin (N = 13,610) was associated with significantly lower risk of VTE in both VTE standard-risk and VTE high-risk groups compared to warfarin (N = 29,303) during 90 days after THA or TKA. Both univariate and multivariate analyses produced the same results.

One retrospective chart review,[30] using data from two large institutions, found that, after adjustment for differences in baseline characteristics, aspirin (N = 8,111; 18.8% bilateral, 81.2% unilateral) was associated with numerically lower rate of VTE (1.5% vs. 2.3%) compared to warfarin (N = 10,840; 19.9% bilateral, 80.1% unilateral) in patients who underwent sequential bilateral TKA; however, the adjusted relative risk for VTE with aspirin was not statistical significant (P = 0.052). Follow-up was 90 days.

PE

One retrospective chart review,[30] using data from two large institutions, found that, after adjustment for differences in baseline characteristics, aspirin (N = 8,111; 18.8% bilateral, 81.2% unilateral) was associated with significantly lower risk of PE compared to warfarin (N = 8,111; 18.8% bilateral, 81.2% unilateral) in patients who underwent sequential bilateral TKA (P = 0.005). The risk of PE was found 204% higher for patients undergoing sequential bilateral TKA compared to those undergoing unilateral TKA.

Safety

Death

One retrospective cohort study[20] found no significant difference in mortality rate between aspirin (N = 243) and warfarin (N = 206) groups during 30 days after TKA or THA.

Bleeding

One retrospective cohort study[20] found no significant difference in the rate of bleeding between aspirin (N = 243) and warfarin (N = 206) groups during 30 days after TKA or THA.

Wound infections/complications

One retrospective cohort study[20] found that aspirin (N = 243) was associated with significant lower risk of surgical site infections compared with warfarin (N = 206) during 30 days after TKA or THA.

One retrospective chart review,[27] using data from three institutions, also found that aspirin (N = 13,610) was associated with significantly lower periprosthetic joint infections compared with warfarin (N = 29,303) during 90 days after THA or TKA in both VTE standard-risk and VTE high-risk groups.

Readmission

One retrospective cohort study[20] found no significant difference in the rate of readmission between aspirin (N = 243) and warfarin (N = 206) groups during 30 days after TKA or THA.

Overall, one retrospective cohort study[20] and two retrospective chart review studies[27,30] provided evidence for the clinical effectiveness and safety of aspirin versus warfarin as VTE prophylaxis in patients undergoing THA or TKA. For clinical effectiveness, aspirin was found to be associated with no significant difference in the rate of VTE,[20] or aspirin was found to be associated with lower risk of VTE[27,30] and PE[30] compared with warfarin. For safety, there were no significant differences between aspirin and warfarin in terms of mortality, bleeding and readmission.[20] Aspirin was found to be associated with significantly lower rate of surgical site infections compared with warfarin. [20,27]

Aspirin versus Another Anticoagulant

The following studies compared aspirin with multiple classes of anticoagulants that were grouped as comparators.

Clinical Effectiveness

VTE

One SR[14] included 13 RCTs comparing aspirin with another anticoagulant, such as rivaroxaban, LMWH (dalteparin, enoxaparin), low molecular weight dextran, heparin, or warfarin. Meta-analysis results showed that there was no significant difference in the risk of VTE between patients receiving aspirin and those receiving another anticoagulant after THA or TKA. Most included RCTs had high risk of bias as assessed by the authors.

One SR[16] included 13 RCTs comparing aspirin with another thromboprophylactic strategy, such as rivaroxaban, warfarin, heparin or placebo. Meta-analysis results showed that there was no significant difference in the risk of VTE between patients receiving aspirin and those receiving another thromboprophylactic strategy after THA or TKA. The quality of the

included RCTs varied from moderate to high on the Jadad scoring as assessed by the authors.

One retrospective chart review,[22] using data from the US MedAssets database, compared aspirin-only (N = 31,176) with another anticoagulant-only (N = 68,339) or combination of anticoagulant and aspirin (N = 11,271) as VTE prophylaxis after THA or TKA. The anticoagulants included unfractionated heparin, LMWH (enoxaparin, dalteparin), fondaparinux, warfarin, and Factor Xa inhibitors (apixaban, rivaroxaban). Aspirin-only was found to be associated with no significant difference in the risk of VTE compared with any anticoagulant (anticoagulant-only or combination of anticoagulant and aspirin) in patients undergoing THA. In patients undergoing TKA, aspirin-only was found to be associated with significantly lower risk of VTE. Propensity score adjustment was used to control for covariates. Follow-up period was 90 days after surgery.

One retrospective chart review,[23] using data from the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI)-participating hospitals, compared aspirin-only (N = 12,831) with another anticoagulant-only (N = 22,620) as VTE prophylaxis after TKA. The anticoagulants included Factor Xa inhibitors, direct thrombin inhibitors, LMWH, synthetic pentasaccharides, or warfarin. Aspirin-only was found to be associated with no significant difference in the risk of composite endpoint of VTE or death as compared with anticoagulant-only, after adjustment for covariates. Aspirin-only was fond to be non-inferior to another anticoagulant with the noninferiority margin specified as 0.3. Follow-up period was 90 days after surgery.

One retrospective case-matched study,[28] after adjusting for propensity scoring, found no significant difference between aspirin (N = 210) and direct oral anticoagulants (N = 210) (i.e., apixaban, rivaroxaban, dabigatran) for the rate of composite endpoint of VTE or bleeding after THA or TKA, after adjustment for covariates.

DVT

The meta-analysis results of 11 RCTs in one SR[14] showed that there was no significant difference in the risk of DVT between patients receiving aspirin and those receiving another anticoagulant, i.e., rivaroxaban, LMWH (dalteparin, enoxaparin), low molecular weight dextran, heparin, or warfarin, after THA or TKA.

One retrospective chart review,[21] using data from a combined Medicare and private-payer Humana database, found that aspirin (N = 649) and Factor Xa inhibitors (N = 1,558) had lowest incidence of DVT (1.7%, 1.7%) followed by enoxaparin (N = 3,377) (2.6%) and warfarin (N = 3,245) (3.7%) after THA. Difference between aspirin and enoxaparin or warfarin was statistically significant ($P < 0.01$). Follow-up period was 90 days after surgery.

One retrospective case-matched study[28] found no significant difference between aspirin (N = 210) and direct oral anticoagulants (N = 210) (i.e., apixaban, rivaroxaban, dabigatran) for the rate of DVT during 90 days after THA or TKA.

PE

The results of meta-analysis of nine RCTs in one SR[14] showed that there was no significant difference in the risk of PE between patients receiving aspirin and those receiving another anticoagulant, i.e., rivaroxaban, LMWH (dalteparin, enoxaparin), low molecular weight dextran, heparin, or warfarin, after THA or TKA.

One retrospective case-matched study[28] found no significant difference between aspirin (N = 210) and direct oral anticoagulants (N = 210) (i.e., apixaban, rivaroxaban, dabigatran) for the rate of PE during 90 days after THA or TKA.

Safety

Death

One SR[16] included 13 RCTs comparing aspirin with another thromboprophylactic strategy, such as rivaroxaban, warfarin, heparin or placebo. Meta-analysis results showed that there was no significant difference in the risk of mortality between patients receiving aspirin and those receiving another thromboprophylactic strategy after THA or TKA.

One retrospective chart review study[25] reviewed data of 31,133 patients who underwent primary total joint arthroplasty (THA, TKA), and found that aspirin (N = 8,0601) was associated with significantly lower risk of death at 30 days, 90 days and one year compared with non-aspirin anticoagulant drug (N = 23,072) (i.e., apixaban, clopidogrel, dabigatran, dipyridamole, enoxaparine, fondaparinux, heparin, lepirudin, rivaroxaban, ticlopidine, and warfarin), after adjustment for covariates.

One retrospective chart review,[26] using data from the American Board of Orthopedic Surgery case database, found that less aggressive VTE prophylaxis (i.e., aspirin and/or sequential compression devices; N = 10,031) was associated with significantly lower rate of mortality compared with more aggressive VTE prophylaxis (i.e., LMWH [enoxaparin], warfarin, rivaroxaban, fondaparinux, or other strategies; N = 12,041) during 90 days after THA or TKA.

Bleeding

One SR[14] included three RCTs comparing aspirin with another anticoagulant, such as rivaroxaban, LMWH (dalteparin, enoxaparin), low molecular weight dextran, heparin, or warfarin. Pooled analysis showed that there was no significant difference in the risk of major bleeding between patients receiving aspirin and those receiving another anticoagulant after THA or TKA.

One SR[16] included 13 RCTs comparing aspirin with another thromboprophylactic strategy, such as rivaroxaban, warfarin, heparin or placebo. Meta-analysis results showed that there was no significant difference in the risk of any bleeding or major bleeding between patients receiving aspirin and those receiving another thromboprophylactic strategy after THA or TKA.

One retrospective chart review,[23] using data from the MARCQI-participating hospitals, compared aspirin-only (N = 12,831) with another anticoagulant-only (N = 22,620) as VTE prophylaxis after TKA. The anticoagulants included Factor Xa inhibitors, direct thrombin inhibitors, LMWH, synthetic pentasaccharides, or warfarin. Aspirin-only was found to be associated with no significant difference in the risk of bleeding as compared with anticoagulant-only. After adjustment for covariates, aspirin was not inferior for a risk of bleeding event when compared with another anticoagulant. The follow-up period was 90 days after surgery.

One retrospective case-matched study[28] found no significant difference between aspirin (N = 210) and direct oral anticoagulants (N = 210) (i.e., apixaban, rivaroxaban, dabigatran) for the rate of any bleeding, major bleeding or clinically overt bleeding during 90 days after

THA or TKA. The rate of transfusion with at least two units of blood was significantly lower in the aspirin group compared to the anticoagulant group.

Wound infections or complications

One SR[14] included three RCTs comparing aspirin with another anticoagulant, such as rivaroxaban, LMWH (dalteparin, enoxaparin), low molecular weight dextran, heparin, or warfarin. Pooled analysis showed that there was no significant difference in the risk of wound infections or other wound complications between patients receiving aspirin and those receiving another anticoagulant after THA or TKA.

One retrospective chart review,[26] using data from the American Board of Orthopedic Surgery case database, found that less aggressive VTE prophylaxis (i.e., aspirin and/or sequential compression devices; N = 10,031) was associated with significantly lower rate of wound infections compared with more aggressive VTE prophylaxis (i.e., LMWH [enoxaparin], warfarin, rivaroxaban, fondaparinux, or other strategies; N = 12,041) after THA or TKA.

Readmission

One retrospective case-matched study[28] found no significant difference between aspirin (N = 210) and direct oral anticoagulants (N = 210) (i.e., apixaban, rivaroxaban, dabigatran) for the rate of readmission during 90 days after THA or TKA.

Overall, two SRs[14,16] and six retrospective studies including five retrospective chart review studies,[21-23,25,26] and one retrospective case matched study,[28] provided evidence for the clinical effectiveness and safety of aspirin compared with another anticoagulant as VTE prophylaxis after THA or TKA. For clinical effectiveness, aspirin was found to be associated with no significant difference in the rate of VTE,[14,16,28] DVT[14,28] or PE[14,28] as compared with another anticoagulant (i.e., apixaban, dabigatran, rivaroxaban, LMWH [enoxaparin, dalteparin], low molecular weight dextran, heparin, warfarin, or placebo). In one study,[22] aspirin was associated with no significant difference in the rate of VTE after THA, but with significant lower rate of VTE after TKA compared with another anticoagulant (i.e., heparin, LMWH, fondaparinux, warfarin, or Factor Xa inhibitors). In another study,[23] aspirin was associated with no significant difference in the risk of composite endpoint of VTE or death compared with another anticoagulant (i.e., Factor Xa inhibitors, direct thrombin inhibitors, LMWH, synthetic pentasaccharides, or warfarin). For safety, there were no significant differences between aspirin and another anticoagulant in terms of death,[16] bleeding,[14,16,23] wound complications,[14] and readmission[28] compared with another anticoagulant (i.e., Factor Xa inhibitors, LMWH [enoxaparin, dalteparin], low molecular weight dextran, heparin, warfarin, direct thrombin inhibitors, synthetic pentasaccharides, or placebo). In other studies, aspirin was associated with significant lower risk of death,[25,26] bleeding[26] and wound infections.[26] compared with another anticoagulant (i.e., apixaban, clopidogrel, dabigatran, dipyridamole, enoxaparine, fondaparinux, heparin, lepirudin, rivaroxaban, ticlopidine, warfarin, fondaparinux, or other strategies).

Guidelines Regarding the Use of Aspirin for VTE prophylaxis

The ASH guideline[33] suggests using aspirin or anticoagulants as VTE prophylaxis for patients undergoing THA or TKA (*Conditional recommendation based on very low certainty in the evidence of effects*).

The NICE guideline[34] recommends aspirin as prophylaxis either as multimodal therapy in THA (i.e., LMWH for 10 days followed by aspirin (75 or 150 mg) for a further 28 days, or as monotherapy in TKA (75 or 150 mg) for 14 days.

The ESA VTE guideline[35] recommends the use of aspirin as an option for VTE prevention in THA or TKA patients without high VTE risk (*Grade 2C*), after low-risk orthopaedic procedures in patients with a high VTE risk or other high-risk orthopaedic procedures in patients without a high VTE risk (*Grade 2C*), or in patients with increased bleeding risk (*Grade 2C*).

Limitations

There were several limitations within the SRs. There was high clinical heterogeneity in the populations assessed (THA, TKA or both), intervention and comparator (dosage and treatment duration of aspirin and anticoagulants), reporting outcomes and adverse events, use of different mechanical prophylaxis devices, and different diagnostic test methods for detection of both asymptomatic and symptomatic DVT or PE, and follow-up duration. Few trials enrolled VTE high-risk patients (i.e., cancer, previous VTE, older age or higher BMI). As assessed by the authors of the SRs, most studies had high risk of bias in at least one domain. Most common biases were blinding and allocation concealment. The quality of evidence for the outcomes, as assessed by the authors, varied among SRs and ranged from very low to high quality.

One of the common limitations among the included primary studies was the retrospective nature design using observational data, which was inherent in selection bias, and could only demonstrate association and not causation. The retrospective analysis in the included studies relied on proper electronic documentation, nature of data source, quality of the data, correct capture of postoperative complications relying on physician and patient reporting, and accuracy of coding. Although nine out of fifteen included studies identified and controlled for potential confounders in their analyses, residual confounders may have been missed and could affect the results. The choice of VTE prophylaxis may have been influenced by the patients' comorbidities or risk factors for VTE, surgeon clinical judgement and institutional preferences, which reflect indication bias. Compliance and adherence to VTE prophylaxis at post-discharge, as well as patients lost to follow-up could not be determined from many databases. The effect of time period on surgical procedure was not assessed, as more recent procedures were likely to have more optimal outcomes due to improvements in techniques over time (e.g., anesthesia, surgical approach, implants, and rapid/same day discharge), which may influence the observed findings.

The NICE guideline[34] did not grade its recommendations. The ASH guideline[33] provided conditional recommendation on the use of aspirin or anticoagulants as VTE prophylaxis after THA or TKA based on very low certainty of the evidence. The ESA guideline[35] graded its recommendations as weak based on low-quality or very low-quality evidence. The recommendations in these guidelines, whose authors were from Canada, US, UK and France, are likely to be applicable to the Canadian settings.

Conclusions and Implications for Decision or Policy Making

This review included five SRs,[13-17] 14 retrospective (nine chart review,[18,21-23,25-27,30,32] three cohort,[19,20,24] two case-matched[28,29]) studies and one prospective cohort study[31] regarding the clinical effectiveness and safety of ASA (i.e., aspirin) for VTE prophylaxis in patients

undergoing THA or TKA, and three guidelines[33-35] regarding the use of ASA in this population.

Compared with LMWH (i.e., enoxaparin, dalteparin), evidence from three SRs[13,14,17] and one retrospective cohort study[19] showed that the use ASA as VTE prophylaxis after THA or TKA was not associated with any significant difference in the rate of VTE, including DVT and PE. There were no significant differences in the rates of bleeding and wound infections or wound complications between the treatment modalities. In one retrospective chart review study,[27] the rates of VTE and periprosthetic joint infections in the ASA group were significantly lower compared to those in the enoxaparin group.

Compared with Factor Xa inhibitors (i.e., rivaroxaban, apixaban), evidence from two SRs[14,15] and three retrospective studies, including one retrospective cohort study,[19] one retrospective case-matched study[29] and one prospective cohort study[31] showed that the use of ASA as VTE chemoprophylaxis in patients undergoing THA or TKA was associated with no significant difference in the rates of VTE, DVT, PE, bleeding, wound complications, and hospital readmission. However, one retrospective chart review study[18] found that ASA was associated with significantly higher risk of VTE, PE, and readmission, but showed no significant difference in terms of DVT, mortality, bleeding, or wound disruption.

Compared with direct thrombin inhibitor (i.e., dabigatran), evidence from one retrospective chart review study[18] showed that ASA was associated with significantly higher risk of VTE after both THA and TKA, and significantly higher risk of DVT and PE after THA, whereas there were no significant differences in the rates of DVT and PE after TKA between the two treatments. There were no significant differences between ASA and dabigatran in the rates of mortality, bleeding, wound disruption and readmission. [18] One retrospective cohort study[24] did not find any significant differences between ASA and dabigatran in terms of clinical effectiveness outcomes (VTE, DVT and PE), or safety outcomes (i.e., death and readmission) after both THA and TKA.

Compared with warfarin, evidence from one retrospective cohort study[20] and two retrospective chart review studies[27,30] showed that the use of ASA as VTE prophylaxis in patients undergoing THA or TKA was associated with no significant difference in the rate of VTE,[20] or ASA was found to be associated with lower risk of VTE[27,30] and PE.[30] Aspirin was found to be associated with no significant differences in the rates of mortality, bleeding and readmission,[20] and with significantly lower rate of surgical site infections.[20,27]

Compared with multiple classes of anticoagulants grouped as a comparator, two SRs[14,16] and six retrospective studies including five retrospective chart review studies,[21-23,25,26] and one retrospective case matched study,[28] showed that ASA did not significantly differ in effectiveness and safety when used for VTE prophylaxis after THA or TKA. ASA was found to be associated with no significant difference in the rate of VTE,[14,16,28] DVT[14,28] PE,[14,28] composite endpoint of VTE or death,[23] death,[16] bleeding,[14,16,23] wound complications,[14] and readmission.[28] In one study,[22] ASA was associated with no significant difference in the rate of VTE after THA, but with significantly lower rate of VTE after TKA. In other studies, ASA was associated with significantly lower risk of death,[25,26] bleeding[26] and wound infections.[26]

The ASH guideline[33] provides conditional recommendation for the use ASA or anticoagulants for VTE prophylaxis in patients undergoing THA or TKA. The NICE guideline[34] recommends ASA for VTE prophylaxis either as monotherapy in TKA or as multimodal therapy in THA. The ESA guideline[35] provides weak recommendations for ASA as an option for VTE prevention in THA or TKA patients without high VTE risk, after low-risk

orthopaedic procedures in patients with a high VTE risk or other high-risk orthopaedic procedures in patients without a high VTE risk, or in patients with increased bleeding risk.

Taken together, the findings of the included studies in this review (i.e., five SRs, 15 primary studies and three guidelines) add to the growing evidence supporting the use of ASA for VTE prophylaxis in patients with or without high VTE risk in the orthopedic setting. Given the limitations of the evidence, interpretations of the findings should be taken with caution, particularly the observations in the retrospective studies, which could only demonstrate association and not causation. Future large and well-designed RCTs are warranted to validate these findings.

Two large multicentre RCTs (the PEPPER trial[36], and the EPCAT III trial[37]) are ongoing.

The PEPPER trial[36] is a randomized open-label clinical trial conducted at 28 US centres that will randomize about 20,000 patients undergoing THA or TKA to ASA (162 mg on day of surgery, then 81 mg twice daily), rivaroxaban (10 mg daily) or warfarin (initial dose based on body weight to achieve an International Normalized Ratio of 2.0) for 30 days right after surgery. Pneumatic compression will be used in conjunction with each treatment during hospital stay. Follow-up period is six months. The primary clinical outcome is a composite of VTE (DVT and PE) and all-cause mortality. The primary safety outcome is bleeding (major, clinical important, wound related). Joint function and patient well-being will also be assessed. The study is expected to complete in 2023.

The EPCAT III trial[37] is a randomized double-blind double-dummy design clinical trial conducted at 15 Canadian centres that will randomize 5,400 patients undergoing THA or TKA to rivaroxaban 10 mg and ASA 81 mg (5 days rivaroxaban followed by 9 days ASA for TKA or 30 days ASA for THA) or ASA-alone 81 mg (14 days aspirin for TKA or 35 days aspirin for THA). Follow-up period is 90 days. The primary outcomes are VTE (DVT or PE) and bleeding (major and clinically relevant, non-major). The secondary outcomes are all-cause death and cost-effectiveness. The study is expected to complete in 2024.

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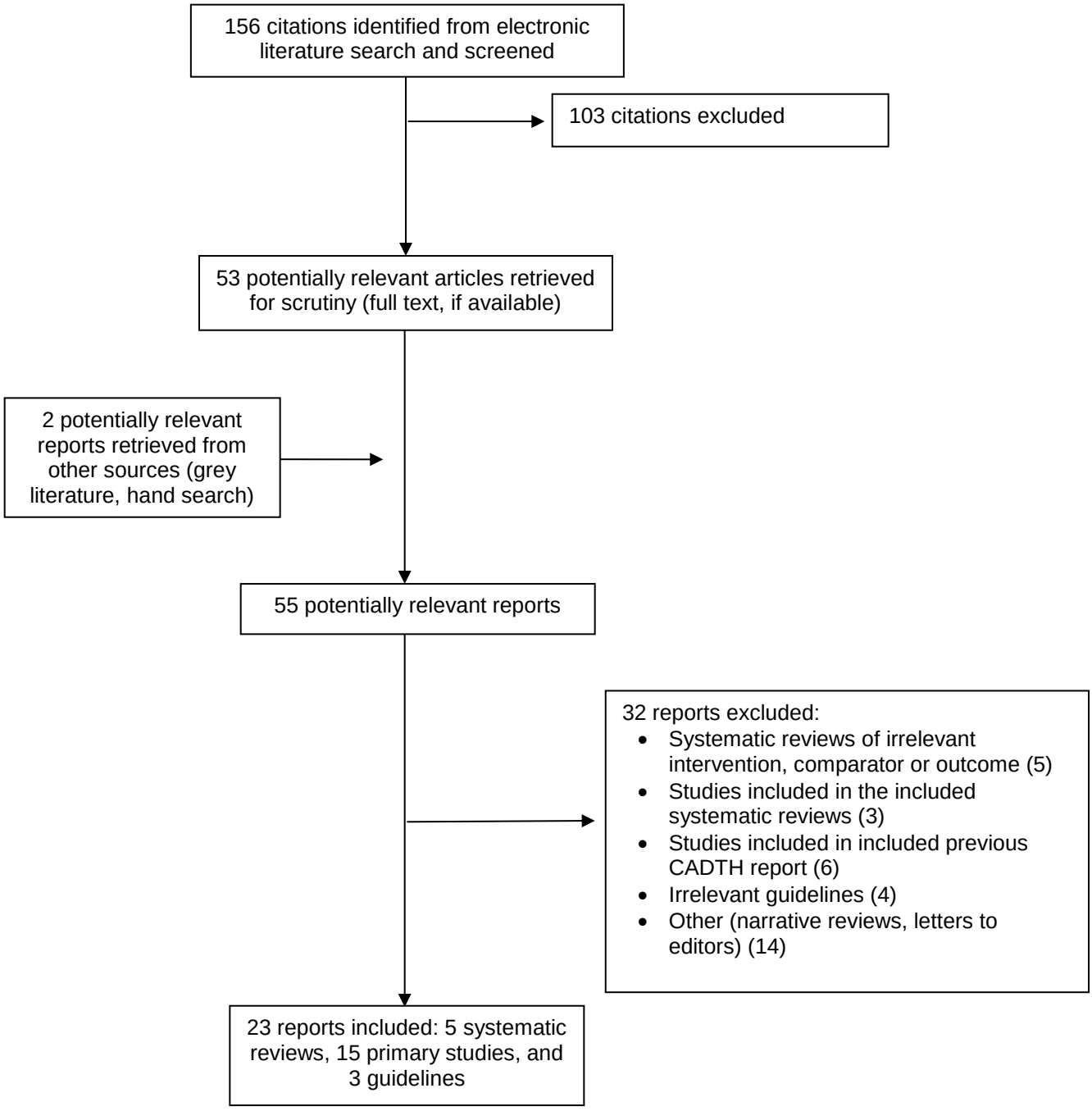
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes and Follow-up
Farey et al., 2020[13] Australia Funding: No financial support	Objective: To compare the efficacy and harms of aspirin and enoxaparin when used as VTE prophylaxis following TKA and THA Total 4 RCTs (N = 1,507) Quality assessment tool: Cochrane risk-of-bias instrument Databases: PubMed, Embase, Medline and CENTRAL from their dates of inception to January 1, 2020 Data analysis: Random-effects meta-analysis.	Adult patients underwent TKA or THA, and received aspirin or enoxaparin as VTE chemoprophylaxis Age: NR Sex or gender: NR	Aspirin (N = 494) Enoxaparin (N = 1,013) Dose: – Aspirin: 100 mg once daily to 325 mg twice daily – Enoxaparin: 40 mg once daily to 30 mg twice daily Treatment duration: two to four weeks	Primary outcomes: – VTE – Mortality Secondary outcomes: – Major bleeding – Minor bleeding – Infections Follow-up: NR
Matharu et al., 2020[14] UK Funding: NR	Objective: To assess the effectiveness and safety of aspirin for VTE prophylaxis after THR or TKR Total 13 RCTs (N = 6,060) Quality assessment tool: Cochrane risk-of-bias instrument Databases: Medline, Embase, Web of Science, and Cochrane Library databases from their dates of inception to September 19, 2019 Data analysis: Random- or fixed-effects meta-analysis.	Adult patients underwent TKA or THA, and received aspirin or another anticoagulant as VTE prophylaxis Mean age: 63.0 years % Male: 42.8	Aspirin (N = 2,969) Another anticoagulant* (N = 3,091) Dose: – Aspirin: Ranged from 81 mg once daily to 650 mg twice daily – Another anticoagulant: Rivaroxaban (10 mg once daily), LMWH (4000 unit once daily), dalteparin (5000 unit once daily), enoxaparin (40 mg once daily), low molecular weight dextran (500 mL once daily), warfarin (7.5 mg or 10 g initially then dose titrated based on prothrombin time) Treatment duration: NR	Primary outcome: – VTE (DVT, PE) Secondary outcomes : – Mortality – Major bleeding – Other bleeding – Wound complications Follow-up: 9 days to 6 months

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes and Follow-up
			* Rivaroxaban, LMWH (dalteparin, enoxaparin), dextran, heparin, warfarin	
Xu et al., 2020[15] Australia Funding: No financial support	Objective: To compare the efficacy of aspirin against rivaroxaban for the prevention of VTE following TKA and THA Total 5 studies (4 RCTs and 1 retrospective cohort study); N = 2,257 Quality assessment tool: Cochrane risk-of-bias instrument Databases: PubMed, Medline, CDSR, DARE and CCTR from their dates of inception to August 2018 Data analysis: Random-effects meta-analysis. Sensitivity analysis was performed by leave-one-out analysis.	Patients receiving aspirin or rivaroxaban for chemoprophylaxis following knee or hip arthroplasty Mean age (years) – Aspirin: 62.7 to 71.2 – Rivaroxaban: 62.7 to 67.1; P = 0.25 % Male – Aspirin: 43.5 – Rivaroxaban: 44 Mean BMI (kg/m^2) – Aspirin: 24.2 to 31.1 – Rivaroxaban: 24.6 to 31.0; P = 0.82	Aspirin (N = 2,257) Rivaroxaban (N = 2,337) Dose: – Aspirin: Ranged from 81 mg daily to 325 mg bi-daily – Rivaroxaban: 10 mg daily in all studies Treatment duration: 9 to 35 days	Primary outcome: – VTE (included DVT and PE) Secondary outcomes: – Bleeding – Readmissions – Wound complications Follow-up: 28 to 90 days
Haykal et al., 2019[16] USA Funding: No financial support	Objective: To evaluate the efficacy and safety of aspirin prophylaxis when compared with placebo or anticoagulants in patients who underwent knee or hip arthroplasty Total 13 RCTs (N = 20,115) Quality assessment tool: Jadad scoring Databases: PubMed, Embase, the Cochrane Collaboration Central of Controlled Trials from their dates of inception to August 2018	Patients receiving aspirin as thromboprophylaxis or another prophylactic modality after TKA or THA Mean age (years) All patients: 67.15 % Male All patients: 24.4	Aspirin (N = 9,673) Another modality* (N = 10, 442) Dose – Aspirin: Ranged from 81 mg daily to 600 mg bi-daily – Another modality: Not specified Treatment duration: 14 to 35 days * new oral anticoagulant, heparin, LMWH or placebo	Primary outcome: – VTE Secondary outcomes: – Mortality – Major bleeding events – Any bleeding events Follow-up: 4 weeks to 1 year

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes and Follow-up
	Data analysis: Random-effects meta-analysis.			
Nadi et al., 2019[17] Australia Funding: the Royal Australian College of Surgeons	Objective: Assess the risks ad benefits of aspirin compared to enoxaparin as VTE prophylaxis for patients undergoing THA or TKA Total 9 RCTs (N = 5,858) Quality assessment tool: Cochrane risk-of-bias instrument Databases: Pubmed, Embase, Cochrane Library databases from their dates of inception to February 21, 2018 Analysis: Random-effects network meta-analysis (NMA). Netrank *p*-scores were generated in the NMA, an indicator for 'best' treatment by ranking the treatments on a continuous scale from 0 to 1.	Patients underwent elective TKA or THA, and received aspirin or enoxaparin as VTE chemoprophylaxis Age range: 21 to 81 years Sex or gender: NR	Aspirin (N = 2,336) Enoxaparin (N = 897) Placebo (N = 2,625) Dose: – Aspirin: 100 mg daily, 325 mg twice daily, or 1200 mg daily – Enoxaparin: 40 to 60 mg daily Treatment duration: NR	Primary outcomes: – DVT – PE Secondary outcomes: – Wound complications – Major bleeding Follow-up: 4 to 24 weeks

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
Matharu et al., 2020[18] UK Funding: NIHR Health Services and Delivery Research programme	Retrospective chart review using data from the National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man between April 2003 and February 2017	Patients who received aspirin or DOAC (dabigatran [direct thrombin inhibitor], rivaroxaban [Factor Xa inhibitor]) after TKA or THA Total: N = 218,650 THA: N = 104,040	THA: Aspirin (N = 28,049) versus dabigatran (N = 28,049) Aspirin (N = 19,021) versus rivaroxaban (N = 19,021) TKA : Aspirin (N = 34,161) versus dabigatran (N = 34,161) Aspirin (N = 25,114) versus rivaroxaban (N = 25,114)		Primary outcome : – VTE (DVT and/or PE) Secondary outcomes: – Length of hospital stay – AEs (readmission, revision

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	Analysis: Propensity score matching, which was generated using logistic regression, was used to control for potential patient and surgical cofounding Factors.	TKA: N = 114,610 Mean age: 69.5 years % Male: 39.3	Dose: NR Treatment duration: NR		surgery, reoperations, mortality, and specific complications) Follow-up: 90 days
Ni Cheallaigh et al., 2020[19] Ireland Funding: No financial support	Retrospective cohort study from a single institution using data recorded between January 1, 2010 and June 30, 2016 Analysis: Non-inferiority analysis of the extended aspirin regimen to modified rivaroxaban regimen based on risk difference for VTE, using a margin of +/-1.0%. Adjustment for covariates was performed using the standardized risk difference estimated with a marginal structural binomial regression.	Patients (N = 5,633) who underwent elective primary TKA or THA received extended aspirin regimen, modified rivaroxaban regimen, or inpatient enoxaparin regimen as VTE prophylaxis Mean age: 65.4 years % Male: 44.7	Extended aspirin (N = 3,460) Regimen: Enoxaparin 40 mg once daily started 12 hour post-operatively for three doses, followed by aspirin 150 mg once daily for 28 days	Modified rivaroxaban (N = 1,212) Regimen: Enoxaparin 40 mg once daily started 12 hour post-operatively for three doses, followed by rivaroxaban 10 mg once daily for 14 days (TKA) or 35 days (THA) Inpatient enoxaparin (N = 961) Regimen: Enoxaparin 40 mg once daily started 12 hour post-operatively, and continued until discharge	– VTE Follow-up: 6 months
Ng et al., 2020[20] USA Funding: No financial support	Retrospective cohort study from a single institution using data recorded between July 1 and December 31, 2014 for the control group, and during 6 months following February	Patients received aspirin or warfarin as VTE prophylaxis after total joint replacement (TKA or THA) Mean age: 63.6 years % Male: 40.8	Aspirin + SCD (N = 243) Dose: 325 mg twice daily Treatment duration: 4 weeks	Warfarin + SCD (N = 206) Dose: INR 2 to 2.5 Treatment duration: 4 weeks	– 30-day postoperative bleeding – VTE – Death – Composite endpoint of VTE and death – Length of hospital stay

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	1, 2015 for the aspirin group. Analysis: Univariable linear mixed effect models, univariable generalized linear mixed effects models were used. Multivariable regression analysis could not be used as too few events.				– 30-day postoperative surgical site infections – Return to operative room Follow-up: 30 days
Bala et al., 2019[21] USA Funding: No financial support	Retrospective chart review using data from a combined Medicare and private -payer Humana database from 2007 to Quarter 1 of 2016 Analysis: No adjustment for covariates was conducted	Patients (N = 8,829) received pharmacologic thromboprophylaxis after THA	Aspirin (N = 649) Dose: NR Treatment duration: NR	Enoxaparin (N = 3,377) Warfarin (N = 3,245) Factor Xa inhibitors (N = 1,558) Dose: NR Treatment duration: NR	– DVT – PE – Bleeding – Utilization Follow-up: 2 weeks, 30 days, 6 weeks, 90 days
Baumgartner et al., 2019[22] USA Funding: Grants from the National Heart, Lung, and Blood Institutes of Health and the University of California Center for Health Quality and Innovation	Retrospective chart review using data from the US MedAssets database between January 1, 2013 and December 31, 2014 Analysis: Patients were divided into three subgroups: aspirin-only, anticoagulants, and aspirin and anticoagulants. Propensity score adjustment was used to control for covariates.	Patients received pharmacologic thromboprophylaxis after TKA or THA Total: N = 110,426 TKA: N = 74,234 from 268 hospitals THA: N = 36,192 from 243 hospitals Age: 18 to ≥ 80 years % Male: TKA: 39.6 THA: 45.4	Aspirin-only Total; N = 31,176 (28.2%) TKA; N = 20,047 (27.0%) THA; N = 10,769 (29.8%) Dose: 80 to 325 mg Treatment duration: NR	Anticoagulant-only Total; N = 68,339 (61.9%) TKA; N = 46,284 (62.4%) THA; N = 22,055 (60.9%) Both anticoagulant and aspirin Total; N = 11,271 (10.2%) TKA; N = 7,903 (10.7%) THA; N = 3,368 (9.3%)	Primary outcome: – VTE Secondary outcomes: – Prosthetic complications – Bleeding events Follow-up: Started at the day of surgery and within 90 days after discharge

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	Propensity scores were estimated using a multivariable regression model, which was developed to model the independent association between aspirin-only (versus anticoagulation) and the risk of postoperative VTE			Dose: Unfractionated heparin (5000 to 7500 units), LMWH (enoxaparin [20 to 40 mg], dalteparin [2500 to 5000 units]), fondaparinux (2.5 mg), warfarin (any dose), and DOACs (apixaban [2.5 mg], rivaroxaban [10 mg]) Treatment duration: NR	
Hood et al., 2019[23] USA Funding: Blue Cross and Blue Shield of Michigan	Retrospective chart review using data from the MARCQI-participating hospitals between April 1, 2013 and October 31, 2015 Analysis: Missing covariates were imputed 10 times using multivariate sequential regression. The final analysis controlled for numerous patients, surgical, and hospital-level variables through inverse probability of treatment weighting. Sensitivity analysis was performed by excluding patients with history of VTE from data set. The noninferiority	Patients (N = 41,537) who underwent TKA in 29 hospitals received none, aspirin only, at least one of five non-aspirin chemoprophylactic agents, and both aspirin and non-aspirin prophylactic agents for VTE prophylaxis Mean age: 65.8 years % Male: 36.1	Aspirin-only (N = 12,831) Dose: NR Treatment duration: NR	None (N = 680) Anticoagulant-only* (N = 22,620) Both aspirin and anticoagulant (N = 5,418) Dose: NR Treatment duration: NR * Direct Factor Xa inhibitors, direct thrombin inhibitors, LMWH, synthetic pentasaccharides, or warfarin.	Primary composite outcome: – Composite VTE (PE, DVT, or death) Secondary outcomes: – Major bleeding event (drop in hemoglobin of 7 g/dL or more) Follow-up: 90 days after surgery

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	margin was specified as 0.3.				
McHale et al., 2019[24] UK Funding: No financial support	Retrospective cohort study using two 6-months data from one institution (May to November 2013 for dabigatran; May to November 2015 for aspirin) Analysis: No adjustment for covariates was performed	Patients received VTE prophylaxis of either aspirin or dabigatran after THA or TKA Total: N = 647 TKA: N = 291 THA: N = 356	Aspirin (N = 301) Dose: 150 mg once daily Treatment duration: 6 weeks after both THA and TKA	Dabigatran (N = 346) Dose: 220 mg once daily Treatment duration: 28 days after THA, or 10 days after TKA	Primary outcome: – 90-day VTE Secondary outcomes: – 90-day all cause mortality – 30-day return to operation room – 30-day readmission Follow-up: 90 days
Rondon et al, 2019[25] USA Funding: Not reported	Retrospective chart review using data from one institution between 2000 and 2017 Analysis: All variables that were associated with mortality (P < 0.2) in the univariate analysis followed by Bonferroni correction were included in a multivariate logistic regression analysis.	Patients (N = 31,133) underwent elective primary total joint arthroplasty (TKA, THA) and received VTE prophylaxis of either aspirin or non-aspirin anticoagulant drug. Mean age: 63.7 years % Male: 45	Aspirin (N = 8,060) Dose: NR Treatment duration: NR	Non-aspirin anticoagulant drug* (N = 23,072) Dose: NR Treatment duration: NR * i.e., apixaban, clopidogrel, dabigatran, dipyridamole, enoxaparine, fondaparinux, heparin, lepirudin, rivaroxaban, ticlopidine, and warfarin	– Mortality Follow-up: 30 days, 90 days and one year
Runner et al., 2019[26] USA Funding: No financial support	Retrospective chart review using data from the American Board of Orthopedic Surgery case database from 2014 to 2016 Analysis: Adjustment for covariates was not performed	Patients received less aggressive VTE prophylaxis (aspirin and/or sequential compression devices) or more aggressive VTE prophylaxis (LMWH [enoxaparin], warfarin, rivaroxaban, fondaparinux, or other strategies) after TKA or THA	Less aggressive VTE prophylaxis (aspirin and/or sequential compression devices); N = 10,031 Dose: NR Treatment duration: NR	More aggressive VTE prophylaxis (LMWH [enoxaparin], warfarin, rivaroxaban, fondaparinux, or other strategies); N = 12,041 Dose: NR Treatment duration: NR	– No complications – Mild thrombotic – Mild bleeding – Moderate thrombotic – Moderate bleeding – Severe thrombotic – Severe bleeding

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
		Total: N = 22,072 TKA: N = 11,489 THA: N = 10,583 Mean age: 64.6 years %Male: NR			– Catastrophic (death within 90 days) Follow-up: 90 days
Tan et al., 2019[27] USA Funding: No source of external funding	Retrospective chart review using data from three institutions between 2000 and 2015 Analysis: Logistic regression was conducted to estimate the probability of patients receiving aspirin compared with warfarin or LMWH on the basis of multiple covariates. Propensity score matching was employed so that the probability of receiving aspirin was similar across thromboembolism prophylaxis groups.	Patients (N = 60,467) at standard-risk or higher-risk of VTE who underwent total joint arthroplasty (TKA, THA) and received VTE prophylactic drugs such as Aspirin, LMWH, or warfarin. Mean age: 63.6 years % Male: 43.4	Aspirin (N = 13,610) Dose: 81 mg or 325 mg twice a day Treatment duration: 4 weeks after surgery Early mobilization was encouraged for all patients. All patients received mechanical compression devices during their hospital stay, and physical therapy began on the day of surgical procedure.	LMWH (N = 17,554) Warfarin (N = 29,303) Dose: Warfarin was titrated against an international normalized ratio target of between 1.8 and 2.0. Dose of LMWH was not reported. Treatment duration: 4 weeks after surgery Early mobilization was encouraged for all patients. All patients received mechanical compression devices during their hospital stay, and physical therapy began on the day of surgical procedure.	Primary outcomes: – VTE Secondary outcome: – Periprosthetic joint infections Follow-up: 90 days after surgery
Yang et al., 2019[28] USA Funding: NR	Retrospective case-matched study using data from one institution database between 2011 and 2015 Analysis: An adjusted logistic	Patients (N = 420) underwent TKA (66%), THA (32%), or hip fracture surgery (2%) and received aspirin or one of the DOACs (apixaban, rivaroxaban, or dabigatran)	Aspirin (N = 210) Dose: 81 mg twice daily, 325 mg daily, 325 mg twice daily Treatment duration: NR	DOACs (N = 210) Dose: Apixaban (2.5 mg daily), dabigatran (220 mg daily), rivaroxaban (10 mg daily)	– Composite endpoint (VTE or bleeding within 90 days of surgery) – VTE – DVT – PE – Bleeding

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	regression model with propensity score added as independent variable was used to evaluate primary endpoint. Sample size calculation was performed.	Mean age: 66.2 years % Male: 45		Treatment duration: NR	– Blood transfusion – Readmission due to bleeding or VTE Follow-up: 90 days
Yuenyongviwat et al., 2019[29] Thailand Funding: The Faculty of Medicine, Prince of Songkla University, Songkla, Thailand	Retrospective case-matched study using data from one institution database between January 2008 and December 2015. Rivaroxaban was used between January 2008 and December 2011, and aspirin was used between January 2012 and December 2015. Analysis: Adjustment for covariates was not performed	Patients (N = 155) who had TKA operated by one surgeon using the same surgical technique and patient care protocol, who chose rivaroxaban between January 2008 and December 2011, and aspirin between January 2012 and December 2015 as VTE prophylaxis. Mean age: 70.7 years %Male: 12.3	Aspirin (N = 79) Dose: 300 mg daily Treatment duration: 14 days	Rivaroxaban (N = 76) Dose: 10 mg daily Treatment duration: 14 days	– DVT or PE – Closed suction drainage output – Blood transfusion – Bleeding Follow-up: 48 hours after surgery
Goel et al., 2018[30] USA Funding: No financial support	Retrospective chart review using data from two large institutions between 2000 and 2017 Analysis: Logistic regression model was used to adjust for differences in baseline characteristics	Patients (N = 18,951) who underwent TKA (19.4% simultaneous bilateral, 80.6% unilateral) and received aspirin or warfarin as VTE prophylaxis. Mean age: 64.3 years % Male: 39.8	Aspirin (N = 8,111); 18.8% bilateral, 81.2% unilateral Dose: 81 mg or 325 mg twice a day Treatment duration: 4 weeks after surgery	Warfarin (N = 10,840); 19.9% bilateral, 80.1% unilateral Dose: Titrated against an international normalized ratio target of between 1.5 and 2.0. Treatment duration: 4 weeks after surgery	– PE – VTE (PE and DVT) Follow-up: 90 days after surgery
Bonutti et al., 2017[31] USA	Six-year prospective cohort study of patients receiving aspirin	Patients who were undergoing TKA by a single orthopaedic surgeon, without	Aspirin and fish oil (N = 300)	Rivaroxaban (N = 250) Dose: NR	– DVT – PE – Bleeding

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
Funding: NR	and mechanical pulsatile stocking (October 2011 to Jue 2013), rivaroxaban (a Factor Xa inhibitor) (June 2013 to December 2014), or aspirin and fish oil (January 2015 to July 2017) Analysis: The odds ratio and 95% confidence interval for VTE and bleeding events was calculated between all three cohort. Adjustment for covariates was not conducted.	history of PE or DVT, and received aspirin and mechanical pulsatile stocking, rivaroxaban, or aspirin and fish oil as VTE prophylaxis Mean age: NR % Male: NR	Aspirin and mechanical pulsatile stocking (N = 300) Dose: 325 mg aspirin; 1,000 mg fish oil Treatment duration: 90 days	Treatment duration: 4 weeks	Follow-up: 90 days after surgery
Chu et al., 2017[32] USA Funding: National Heart, Lug, and Blood Institute of the National Institutes of Health, and the University of California Center for Health quality and Innovation	Retrospective chart review using multi-institutional data between 2009 and 2012 Analysis: Propensity scores were developed to model the likelihood of a patient receiving aspirin-only therapy. Multivariable logistic regression models with included propensity scores were used to test the association of VTE with aspirin-only exposure. Variables corresponding to patient	Patients who underwent TKA (N = 231,780) and THA (N = 110, 621), and who received aspirin or anticoagulant as VTE prophylaxis. Age: 18 to ≥ 80 years % Male: 39.3	Aspirin only (N = 17,443) Dose: NR Duration of treatment: First 7 days after surgery	Anticoagulant only (n = 184,790) Both anticoagulant and aspirin (n = 29,547) Dose: Warfarin (any dose), injectable heparin (between 5,000 and 7,500 units), LMWH (enoxaparin at 30 mg or 40 g, dalteparin at 2,500 or 5,000 units, or tinzaparin at 3,500 or 4,500 units); fondaparinux at 2.5 mg; or direct oral anticoagulants	– VTE (PE or DVT) Follow-up: During the index hospitalization or within 30 days of the index surgery

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	demographics, hospital characteristics, comorbidity, and VTE risk score were included in the model as potential adjustors.			(dabigatran 75 mg or 150 mg, rivaroxaban 10 mg, or apixaban 2.5 mg) Duration of treatment: First 7 days after surgery	

DVT = deep vein thrombosis; INR = international normalized ratio; MARCQI = the Michigan Arthroplasty Registry Collaborative Quality Initiative; NR = not reported; PE = pulmonary embolism; SCD = sequential compression device; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism;

Table 4: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
ASH, Anderson et al., 2019[33] Canada and USA Funding: ASH	Intended users: All healthcare professionals involved in decision making about preventing VTE in patients undergoing surgery Target population: Patients undergoing major surgery including THA and TKA	Modalities for the preventions of VTE (pharmacological antithrombotic prophylaxis and mechanical prophylaxis)	Outcomes related to clinical efficacy and safety of each modality for the prevention of VTE	Systematic methods used to search for evidence, selection and synthesis. A comprehensive review of the evidence was performed.	The panel included surgeons with subspecialty representation, hematologists, internists, and a pharmacist, all of who had clinical and research expertise on the guideline topic. The panel also included methodologists with expertise in evidence appraisal and guideline development and two patient representatives. The panel reviewed the evidence, used GRADE approach to assess evidence, and make recommendations. Recommendations were graded based on the certainty of evidence as high, moderate, low or very low	The guideline was peer-reviewed

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
NICE 2019[34] UK Funding: Department of Health in the UK	Intended users: Healthcare professionals Target population: Adults and young people aged 16 and over admitted to hospital or attending hospital for day procedures	Modalities for reducing the risk of VTE in people over 16 years of age admitted to hospitals	Clinical, economic and safety outcomes of VTE prophylaxis options and patient preferences.	Systematic methods were used to search for evidence. GRADE approach was used for assessing and rating the quality of evidence.	Committee members developed review questions, reviewed research evidence, incorporate economic evaluation, linked to other guidance, and wrote recommendations. No grading of recommendations was provided.	The draft version of the guideline was posted on the NICE website for consultation with registered stakeholders.
ESA VTE Guidelines Task Force, Jenny et al., 2018[35] France Funding: ESA	Intended users: Healthcare professionals Target population: Patients undergoing major surgery including THA and TKA	Aspirin	Outcomes related to clinical efficacy, safety, harms and cost-effectiveness of aspirin in the prevention of VTE	Systematic methods used to search for evidence, selection and synthesis. A comprehensive review of the evidence was performed.	The Task Force nominated experts responsible for the development of the guidelines. They reviewed the evidence, used GRADE approach to assess evidence, and make recommendations, which were graded based on level of evidence.[a]	The guideline was peer-reviewed

ASH = American Society of Hematology; GRADE = the Grading of Recommendations Assessment, Development and Evaluation; ESA = European Society of Anesthesiology; NR = not reported; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism

[a]**Strength of recommendation:**
Grade 1A: Strong recommendation, high-quality evidence
Grade 1B: Strong recommendation, moderate-quality evidence
Grade 1C: Strong recommendation, low-quality or very low-quality evidence
Grade 2A: Weak recommendation, high-quality evidence
Grade 2B: Weak recommendation, moderate-quality evidence
Grade 2C: Weak recommendation, low-quality or very low-quality evidence

Level of evidence:
RCTs without important limitations or overwhelming evidence from observational studies
RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Observational studies or case series
RCTs without important limitations or overwhelming evidence from observational studies
RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Observational studies or case series

Appendix 3: Critical Appraisal of Included Publications

Table 5: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[9]	Farey et al., 2020[13]	Matharu et al., 2020[14]	Xu et al., 2020[15]	Haykal et al., 2019[16]	Nadi et al., 2019[17]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	No	No	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No	No	No	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes

AMSTAR 2 Checklist[9]	Farey et al., 2020[13]	Matharu et al., 2020[14]	Xu et al., 2020[15]	Haykal et al., 2019[16]	Nadi et al., 2019[17]
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA (due to low number of studies)	Yes	NA (due to low number of studies)	NA (due to low number of studies per comparison)	NA (due to low number of studies)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; NA = not applicable; PICO = Population, Intervention, Comparator, and Outcome; RoB = risk of bias.

Table 6: Quality Assessment of Non-Randomized Studies

Downs and Black Critical Appraisal Checklist[10]	Matharu et al., 2020[18]	Ni Cheallaigh et al., 2020[19]	Ng et al., 2020[20]	Bala et al., 2019[21]	Baumgartner et al., 2019[22]	Hood et al., 2019[23]	McHale et al., 2019[24]
Reporting	--	--	--	--	--	--	--
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes	No	Yes	Yes	Yes
4. Are the interventions of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes	Yes	Yes	No	Yes	Yes	Yes
6. Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes (95% CI provided)	Yes (95% CI provided)	Yes (95% CI provided)	No	Yes (95% CI provided)	Yes (SD and 95% CI provided)	No
8. Have all important adverse events that may be a consequence of the intervention being reported?	Yes	No	Yes	Yes	Yes	Yes	Yes
9. Have the characteristics of patients lost to follow-up been described?	NA	NA	NA	NA	NA	NA	NA

Downs and Black Critical Appraisal Checklist[10]	Matharu et al., 2020[18]	Ni Cheallaigh et al., 2020[19]	Ng et al., 2020[20]	Bala et al., 2019[21]	Baumgartner et al., 2019[22]	Hood et al., 2019[23]	McHale et al., 2019[24]
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
External validity	--	--	--	--	--	--	--
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	NA (Database review)	NA (Database review)	NA (Chart review)	NA (Database review)	NA (Database review)	NA (Database review)	NA (Chart review)
12. Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	NA (Database review)	NA (Database review)	NA (Chart review)	NA (Database review)	NA (Database review)	NA (Database review)	NA (Chart review)
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity – bias	--	--	--	--	--	--	--
14. Was an attempt made to blind study subjects to the intervention they have received?	NA	NA	NA	NA	NA	NA	NA
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	NA	NA	NA	NA	NA	NA
16. If any of the results of the study were based on “data dredging”, was this made clear?	NA	NA	NA	NA	NA	NA	NA
17. In trials and cohort studies, so the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (same follow-up)	Yes (same follow-up)	Yes (same follow-up)	Unclear (follow-up NR)	Yes (same follow-up)	Yes (same follow-up)	Yes (same follow-up)
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Was compliance with the intervention/s reliable?	NA	NA	NA	NA	NA	NA	NA

Downs and Black Critical Appraisal Checklist[10]	Matharu et al., 2020[18]	Ni Cheallaigh et al., 2020[19]	Ng et al., 2020[20]	Bala et al., 2019[21]	Baumgartner et al., 2019[22]	Hood et al., 2019[23]	McHale et al., 2019[24]
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity – confounding (selection bias)	--	--	--	--	--	--	--
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	No (different populations)	Yes	Yes	Yes	No (different populations)
22. Were study subjects in different intervention groups (trial and cohort studies) or were the cases and controls (case-controls studies) recruited over the same period of time?	Yes	Yes	No (different period of time)	Yes	Yes	Yes	No (different period of time)
23. Were study subjects randomized to intervention groups?	NA	NA	NA	NA	NA	NA	NA
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA
25. Was the adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Yes	No (but no significant difference in covariates between groups)	No	Yes	Yes	No
26. Were losses of patients to follow-up taken into account?	NA	NA	NA	NA	NA	NA	NA
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)	NR	Yes	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)	NR

AEs = adverse events; CI = confidence interval; ED = emergency department; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation.

Table 7: Quality Assessment of Non-Randomized Studies (Continued)

Downs and Black Critical Appraisal Checklist[10]	Rondon et al., 2019[25]	Runner et al., 2019[26]	Tan et al., 2019[27]	Yang et al., 2019[28]	Yueny ongvi wat et al., 2019[29]	Goel et al., 2018[30]	Bonutti et al., 2017[31]	Chu et al., 2017[32]
Reporting	--	--	--	--	--	--	--	--
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	No	Yes	Yes	Yes	Partiall y	No	Yes
4. Are the interventions of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes	No	Yes	Yes	Yes	Yes	No	Yes
6. Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes (SD provided)	No	Yes (95% CI provide d)	No	No	Yes (95% CI provide d)	Yes (95% CI provided)	Yes (95% CI provided)
8. Have all important adverse events that may be a consequence of the intervention being reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Have the characteristics of patients lost to follow-up been described?	NA	NA	NA	NA	NA	NA	NA	NA
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
External validity	--	--	--	--	--	--	--	--
11. Were the subjects asked to participate in the study representative of the entire	NA (Database review)	NA (Database review)	NA (Datab ase review)	NA (chart review)	NA (chart review)	NA (Datab ase review)	Probably yes (6-year prospective study	NA (Database review)

Downs and Black Critical Appraisal Checklist[10]	Rondon et al., 2019[25]	Runner et al., 2019[26]	Tan et al., 2019[27]	Yang et al., 2019[28]	Yueny ongvi wat et al., 2019[29]	Goel et al., 2018[30]	Bonutti et al., 2017[31]	Chu et al., 2017[32]
population from which they were recruited?							enrolling three groups consecutiv ely)	
12. Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	NA (Database review)	NA (Database review)	NA (Datab ase review)	NA (chart review)	NA (chart review)	NA (Datab ase review)	Unclear	NA (Database review)
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity – bias	--	--	--	--	--	--	--	--
14. Was an attempt made to blind study subjects to the intervention they have received?	NA	NA	NA	NA	NA	NA	NA	NA
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	NA	NA	NA	NA	NA	NA	NA
16. If any of the results of the study were based on “data dredging”, was this made clear?	NA	NA	NA	NA	NA	NA	NA	NA
17. In trials and cohort studies, so the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (same follow-up)	Yes (same follow-up)	Yes (same follow-up)	Yes (same follow-up)	Yes	Yes (same follow-up)	Yes (same follow-up)	Yes (same follow-up)
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Was compliance with the intervention/s reliable?	NA	NA	NA	NA	NA	NA	NA	NA
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Downs and Black Critical Appraisal Checklist[10]	Rondon et al., 2019[25]	Runner et al., 2019[26]	Tan et al., 2019[27]	Yang et al., 2019[28]	Yueny ongvi wat et al., 2019[29]	Goel et al., 2018[30]	Bonutti et al., 2017[31]	Chu et al., 2017[32]
Internal validity – confounding (selection bias)	--	--	--	--	--	--	--	--
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
22. Were study subjects in different intervention groups (trial and cohort studies) or were the cases and controls (case-controls studies) recruited over the same period of time?	Yes	Yes	Yes	Yes	No	Yes	No (Three groups were enrolled consecutively at three different time periods	Yes
23. Were study subjects randomized to intervention groups?	NA	NA	NA	NA	NA	NA	NA	NA
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA	NA
25. Was the adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	No	Yes	Yes	No (but no significant differences in covariates)	Yes	No	Yes
26. Were losses of patients to follow-up taken into account?	NA	NA	NA	NA	NA	NA	NA	NA
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)	Yes	NR	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)	NR, but probably yes (large cohort)

AEs = adverse events; CI = confidence interval; ED = emergency department; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation.

Table 8: Quality Assessment of Guidelines

AGREE II checklist[11]	ASH, Anderson et al., 2019[33]	NICE, 2019[34]	ESA VTE Guidelines Task Force, Jenny et al., 2018[35]
Scope and purpose	--	--	--
1. Objectives and target patient population were explicit	Yes	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes	Yes
3. The population to whom the guideline is meant to apply is specifically described	Yes	Yes	Yes
Stakeholder involvement	--	--	--
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes
5. The views and preferences of the target population have been sought	Yes	Yes	Unclear
6. The target users of the guideline are clearly defined	Yes	Yes	Yes
Rigour of development	--	--	--
7. Systematic methods were used to search for evidence	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes	Yes	Yes
14. A procedure for updating the guideline is provided	Yes	Yes	Yes
Clarity of presentation	--	--	--
15. The recommendations are specific and unambiguous	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes	Yes
Applicability	--	--	--
18. The guideline describes facilitators and barriers to its application	Yes	Yes	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Yes	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered	Yes	Yes	Yes

AGREE II checklist[11]	ASH, Anderson et al., 2019[33]	NICE, 2019[34]	ESA VTE Guidelines Task Force, Jenny et al., 2018[35]
21. The guideline presents monitoring and/or auditing criteria	Yes	Yes	Yes
Editorial independence	--	--	--
22. The views of the funding body have not influenced the content of the guideline	Yes	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes

ASH = American Society of Hematology; ESA = European Society of Anesthesiology; VTE = venous thromboembolism.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 9: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Farey et al., 2020[13]	
Aspirin vs. enoxaparin (a LMWH) – TKA or THA Quality of included studies (4 RCTs) assessed by the authors: – The included trials had significant risk of bias. Quality of evidence assessed by the authors: – For VTE, PE, DVT: Low to very low – For bleedings: Moderate to very low *Clinical effectiveness:* VTE (4 RCTs) – RR (95% CI) = 0.84 (0.41 to 1.75); I^2 = 71%; P = 0.65 PE (2 of 3 RCTs estimable) – RR (95% CI) = 1.01 (0.14 to 7.21); I^2 = 0%; P = 0.99 DVT (4 RCTs) – RR (95% CI) = 0.85 (0.43 to 1.71); I^2 = 68%; P = 0.65 *Safety:* Major bleeding (2 of 3 RCTs estimable) – RR (95% CI) = 0.84 (0.08 to 9.16); I^2 = 20%; P = 0.89 Minor bleeding (3 RCTs) – RR (95% CI) = 0.77 (0.34 to 1.72); I^2 = 41%; P = 0.52	*"There is currently a lack of high quality randomized controlled trials supporting the use of aspirin as VTE chemoprophylaxis in the initial postoperative period for both total hip and total knee arthroplasty. The results of this meta-analysis provide cautious endorsement for the position that aspirin is likely a safe alternative to enoxaparin for TKA patients as part of a multimodal enhanced recovery protocol, but care is advised for THA patients owing to a lack of data from trials. Current evidence from randomized controlled trials is generally of low quality, and does not estimate critical event data for VTE incidence or mortality, as well as major and minor bleeding events with sufficient certainty."*[13] (p. 1 to 2)
Matharu et al., 2020[14]	
Aspirin vs. another anticoagulants (Rivaroxaban, LMWH [dalteparin, enoxaparin], dextran, heparin, warfarin) – TKA or THA Quality of included studies (13 RCTs) assessed by the authors: – 11 trials had high risk of bias. Most common biases were blinding of participants and personnel, blinding of outcome assessment, and allocation concealment. Two trials had low risk of bias. Quality of evidence for VTE, DVT, PE, and wound hematoma assessed by the authors: – Low to high *Clinical effectiveness:* VTE – Aspirin versus all groups (13 RCTs): RR (95% CI) = 1.12 (0.78 to 1.62); I^2 = 63% – Aspirin vs. LMWH (5 RCTs): RR (95% CI) = 0.76 (0.37 to 1.56) – Aspirin vs. rivaroxaban (3 RCTs): RR (95% CI) = 1.52 (0.56 to 4.12)	*"In terms of clinical effectiveness and safety profile, aspirin did not differ statistically significantly from other anticoagulants used for VTA prophylaxis after THR ad TKR. Future trials should focus on noninferiority analysis of aspirin compared with alternative anticoagulants and cost-effectiveness."*[14] (p. 376)

Main Study Findings	Author's Conclusions
DVT – Aspirin vs. all groups (11 RCTs): RR (95% CI) = 1.04 (0.72 to 1.51) – Aspirin vs. LMWH (5 RCTs): RR (95% CI) = 0.83 (0.42 to 1.63) – Aspirin vs. rivaroxaban (3 RCTs): RR (95% CI) = 1.67 (0.53 to 5.26) PE – Aspirin vs. all groups (9 RCTs): RR (95% CI) = 1.01 (0.68 to 1.48) – Aspirin vs. LMWH (5 RCTs): RR (95% CI) = 0.71 (0.19 to 2.61) *Safety:* No significant differences between aspirin and other anticoagulant groups for: – Hematoma (5 RCTs) – Major bleeding (3 RCTs) – Wound infections (3 RCTs) – Other wound complications (3 RCTs)	
Xu et al., 2020[15]	
Rivaroxaban (a Factor Xa inhibitor) versus Aspirin – TKA or THA Quality of included studies (5 studies) assessed by the authors: – All studies had low to unclear risk of bias for random sequence generation, blinding of outcome assessment, incomplete outcome data and selective reporting. *Clinical effectiveness:* VTE (DVT and PE) – DVT rate (4 studies): RR (95% CI) = 0.67 (0.28 to 1.76); I^2 = 58%; P = 0.44 – PE rate (2 studies): RR (95% CI) = 0.99 (0.38 to 2.59); I^2 = 0%; P = 0.98 – Any VTE rate (4 studies): RR (95% CI) = 0.73 (0.31 to 1.75); I^2 = 60%; P = 0.48 *Safety:* Bleeding – Major bleeding (2 studies): RR (95% CI) = 0.39 (0.10 to 1.52); I^2 =34%; P = 0.17 – Any bleeding (2 studies): RR (95% CI) = 1.3 (0.45 to 3.79); I^2 = 81%; P = 0.62 Readmissions – Rate (2 studies): RR (95% CI) = 0.80 (0.50 to 1.30); I^2 = 0%; P = 0.37 Wound complications – Rate (3 studies): RR (95% CI) = 2.0 (0.73 to 5.55); I^2 = 0%; P = 0.17	*"Aspirin was not significantly different to rivaroxaban for prevention of VTE or adverse events after TKA or THA. However, this study was limited by significant heterogeneity of the included studies. More large randomized studies are needed to add to this body of evidence."*[15] (p. 1)
Haykal et al., 2019[16]	
Aspirin vs. other thromboprophylactic strategy (Placebo, rivaroxaban, warfarin, or heparin) – TKA or THA Quality of included studies (13 RCTs) assessed by the authors:	*"Among patients who underwent knee or hip arthroplasty, aspirin prophylaxis was found to be associated with similar efficacy and safety with anticoagulants. When compared with placebo, aspirin*

Main Study Findings	Author's Conclusions
On the Jadad scoring, one study scored 2 (low), five studies scored 3 (moderate), and seven studies scored 5 (high) *Clinical effectiveness:* VTE – Aspirin versus all groups (13 RCTs): RR (95% CI) = 0.87 (0.86 to 1.11); I^2 = 73%; P = 0.43 – Aspirin versus placebo (5 RCTs): RR (95% CI) = 0.65 (0.47 to 0.89); I^2 = 44%; P = 0.008 *Safety* Mortality – Aspirin vs. all groups (6 of 13 RCTs estimable): RR (95% CI) = 0.98 (0.86 to 1.11); I^2 = 0%; P = 0.84 – Aspirin versus placebo (2 of 5 RCTs estimable): RR (95% CI) = 0.97 (0.86 to 1.11); I^2 = 0%; P = 0.34 Major bleeding events – Aspirin vs. all groups (7 of 13 RCTs estimable): RR (95% CI) = 0.96 (0.50 to 1.84); I^2 = 27%; P = 0.22 – Aspirin vs. placebo (2 of 5 RCTs estimable): RR (95% CI) = 0.57 (0.15 to 2.17); I^2 = 43%; P = 0.18 Any bleeding events – Aspirin vs. all groups (8 RCTs of 13 RCTs estimable): RR (95% CI) = 1.09 (0.82 to 1.44); I^2 = 48%; P = 0.06 – Aspirin vs. placebo (2 of 5 RCTs estimable): RR (95% CI) = 0.98 (0.43 to 2.24); I^2 = 49%; P = 0.16	*prophylaxis was associated with significantly reduced VTE and a comparable safety profile."*[16] (p. 294)
Nadi et al., 2019[17]	
Aspirin vs. enoxaparin (a LMWH) – TKA or THA Quality of included studies (9 RCTs) assessed by the authors: – High risk of bias for blinding, which was difficult to maintain because enoxaparin was given subcutaneously while aspirin was given orally. – Three RCTs blinded effectively by using placebo injection and placebo tablets. Quality of evidence assessed by the authors: – For PE, DVT: Low to very low – For bleedings and wound complications: Moderate to very low *Clinical effectiveness:* Total DVT – Direct evidence (2 RCTs): RR (95% CI) = 1.27 (0.84 to 1.96) – Indirect evidence (7 RCTs): RR (95% CI) = 1.09 (0.56 to 2.12) – NMA (9 RCTs): RR (95% CI) = 1.27 (0.84 to 1.96) – Netrank *p*-scores: 0.94 vs. 0.55 Symptomatic PE – NMA (2 RCTs): RR (95% CI) = 1.02 (0.0 to 242.90)	*"This review did not find statistically significant differences between aspirin and enoxaparin. Future studies should identify more evidence, particularly for rare outcomes such as PE, as this might help decision-makers to get consensus on the use of aspirin s VTE prophylaxis."*[17] (p. 1204)

Main Study Findings	Author's Conclusions
– Netrank *p*-scores: 0.68 vs. 0.44 *Safety:* Major bleeding – Indirect evidence (7 RCTs): RR (95% CI) = 0.97 (0.02 to 50.99) – NMA (7 RCTs): RR (95% CI) = 0.97 (0.02 to 50.99) – Netrank *p*-scores: 0.51 vs. 0.50 Wound complications – Direct evidence (1 RCT): RR (95% CI) = 0.68 (0.12 to 3.98) – Indirect evidence (1 RCT): RR (95% CI) = 0.66 (0.05 to 8.86) – NMA (2 RCTs): RR (95% CI) = 0.73 (0.17 to 3.20) – Netrank *p*-scores: 0.79 vs. 0.46	

CI = confidence interval; DVT = Deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; RR = risk ratio; THA = total hip arthroplasty; TKA = total knee arthroplasty; vs. = versus; VTE = venous thromboembolism.

Table 10: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Matharu et al., 2020[18]	
DOACs (thrombin inhibitors and Factor Xa inhibitors) vs. aspirin – after 90 days of TKA or THA **After THA,** *Clinical effectiveness:* VTE (DVT and/or PE) – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.69 (0.55 to 0.87); **P = 0.002** – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.63 (0.47 to 0.85); **P = 0.003** DVT only – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.72 (0.53 to 0.99); **P = 0.041** – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.76 (0.50 to 1.16); P = 0.207 PE only – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.69 (0.49 to 0.96); **P = 0.026** – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.60 (0.40 to 0.90); **P = 0.013** *Safety:* Short-term revision surgery – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.96 (0.72 to 1.27); P = 0.773 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.94 (0.67 to 1.32); P = 0.732 Mortality – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.99 (0.72 to 1.36); P = 0.935 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.73 (0.49 to 1.10); P = 0.129 Readmissions – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.95 (0.90 to 1.01); P = 0.068 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.91 (0.85 to 0.97); **P = 0.003**	*"After THA and TKA, DOACs were associated with a reduced risk of VTE compared with aspirin. DOACs were associated with a reduced length of stay, and DOACs were not associated with an increase in the risk of further surgery, wound problems, bleeding complications, or mortality compared with aspirin."*[18] (p. 1)

Main Study Findings	Author's Conclusions
Reoperations – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.02 (0.69 to 1.51); P = 0.920 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 1.26 (0.81 to 1.98); P = 0.306 Wound disruption – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.95 (0.61 to 1.49); P = 0.819 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.87 (0.52 to 1.46); P = 0.600 Surgical site infections – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.04 (0.84 to 1.28); P = 0.709 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.91 (0.70 to 1.17); P = 0.441 Major bleeding – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.10 (0.67 to 1.80); P = 0.706 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.93 (0.54 to 1.60); P = 0.782 Blood transfusion – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.77 (0.43 to 1.38); P = 0.378 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.68 (0.34 to 1.39); P = 0.292 Acute renal failure – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.32 (0.94 to 1.85); P = 0.106 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 1.87 (1.30 to 2.68); **P = 0.001** Myocardial infarction – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.75 (0.48 to 1.18); P = 0.212 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.52 (0.29 to 0.92); **P = 0.026** Length of stay – Thrombin inhibitors vs. aspirin: Coefficient (95% CI) = -0.37 d (-0.43 to -0.31); **P < 0.001** – Factor Xa inhibitors vs. aspirin: Coefficient (95% CI) = -0.80 d (-0.87 to -0.74); **P < 0.001** **After TKA,** *Clinical effectiveness:* VTE – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.82 (0.68 to 0.98); **P = 0.032** – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.73 (0.58 to 0.91); **P = 0.006** DVT only – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.83 (0.64 to 1.07); P = 0.148 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.81 (0.58 to 1.14); P = 0.231 PE only – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.83 (0.64 to 1.06); P = 0.139 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.67 (0.49 to 0.91); **P = 0.011** *Safety:* Short-term revision surgery – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.21 (0.74 to 2.00); P = 0.447 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 1.65 (0.95 to 2.88); P = 0.077	

Main Study Findings	Author's Conclusions
Mortality – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.30 (0.87 to 1.92); P = 0.197 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.72 (0.42 to 1.23); P = 0.227 Readmissions – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.02 (0.97 to 1.06); P = 0.465 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.95 (0.90 to 0.77); **P = 0.046** Reoperations – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.01 (0.73 to 1.41); P = 0.933 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.98 (0.66 to 1.45); P = 0.921 Wound disruption – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.06 (0.79 to 1.43); P = 0.702 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 1.07 (0.75 to 1.51); P = 0.722 Surgical site infections – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.09 (0.93 to 1.27); P = 0.269 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.91 (0.75 to 1.11); P = 0.355 Major bleeding – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.02 (0.71 to 1.46); P = 0.926 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.91 (0.59 to 1.40); P = 0.659 Blood transfusion – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.72 (0.35 to 1.47); P = 0.371 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.38 (0.15 to 0.96); **P = 0.040** Acute renal failure – Thrombin inhibitors vs. aspirin: OR (95% CI) = 1.26 (0.95 to 1.67); P = 0.113 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 1.70 (1.24 to 2.32); **P = 0.001** Myocardial infarction – Thrombin inhibitors vs. aspirin: OR (95% CI) = 0.91 (0.59 to 1.39); P = 0.663 – Factor Xa inhibitors vs. aspirin: OR (95% CI) = 0.87 (0.52 to 1.46); P = 0.600 Length of stay – Thrombin inhibitors vs. aspirin: Coefficient (95% CI) = -0.43 d (-0.48 to -0.38); **P < 0.001** – Factor Xa inhibitors vs. aspirin: Coefficient (95% CI) = -0.84 d (-0.90 to -0.79); **P < 0.001**	
Ni Cheallaigh et al., 2020[19]	
Extended aspirin regimen vs. Modified rivaroxaban regimen vs. Inpatient enoxaparin regimen – after 6 months of TKA or THA *Clinical effectiveness* Total VTE (DVT and/or PE) – Extended aspirin regimen: 1.04% – Modified rivaroxaban regimen: 0.66% – Inpatient enoxaparin regimen: 1.04%	*"In daily clinical practice, extended aspirin regimen is at least as effective as modified rivaroxaban for preventing clinically important venous thromboembolism among patients undergoing hip or knee arthroplasty who are discharged from the hospital without complications."*[19] (p. 853)

Main Study Findings	Author's Conclusions
– Difference (90%TOST CI) between aspirin and rivaroxaban = 0.38% (-0.096% to 0.86%); CI falls with the margin interval of +/-1%, suggesting equivalence between the two treatments. – Difference (90%TOST CI) between aspirin and enoxaparin or rivaroxaban = 0.12% (-0.28% to 0.52%); CI falls with the margin interval of +/-1%, suggesting equivalence between the two treatments.	
Ng et al., 2020[20]	
Aspirin + SCD vs. Warfarin + SCD – after 30 days of TKA or THA *Clinical effectiveness:* – VTE: 0.8% vs. 0.5%; P = 0.67 Composite end point (VTE or death): 1.6% vs.1.0%; P = 0.54 *Safety:* – Death within 30 days: 0.8% vs. 0.5%; P = 0.67 – Bleeding: 1.2% vs. 2.9%; P = 0.22 – Surgical site infections: 1.2% vs. 5.8%; **P = 0.02** (Aspirin was associated with 0.2 times [95% CI 0.06 to 0.74] as likely to experience a surgical site infections) – Acute kidney injury/acute kidney failure: 0.4% vs. 0.5%; P = 0.91 – Readmissions within 30 days: 2.4% vs. 5.8%; P = 0.09 – Unplanned return to operating room: 0.4% vs. 3.9%; **P = 0.03** (OR [95% CI] = 1.10 [0.01 to 0.84]) – Length of stay, days, mean (SE): 3.35 (0.21) vs. 5.56 (0.22); P = 0.35	*"A simplified risk-stratified protocol used to choose patients for aspirin 325 mg twice-daily therapy is safe and effective in patients undergoing total joint replacement, and surgical site infections and return to operating room rates may be lower when compared to universal warfarin therapy."*[20] (p. 443)
Bala et al., 2019[21]	
Aspirin vs. enoxaparin, warfarin, or Factor Xa inhibitors – after 90 days of THA *Clinical effectiveness:* DVT at 90 days (Significant difference among the agents, **P < 0.01**) – Aspirin: 1.7% – Enoxaparin: 2.6% – Warfarin: 3.7% – Factor Xa inhibitors: 1.7% PE at 90 days (Not applicable to determine difference statistically among the agents) – Aspirin: < 2% – Enoxaparin: 0.4% – Warfarin: 0.7% – Factor Xa inhibitors: < 1% *Safety:* Anaemia at 90 days (Significant difference among the agents, **P = 0.01**) – Aspirin: 24% – Enoxaparin: 26% – Warfarin: 25% – Factor Xa inhibitors: 26% Transfusion at 90 days (Significant difference among the agents, **P < 0.01**) – Aspirin: 12%	*"The utilization of aspirin and Factor Xa inhibitors increased over time. Aspirin and Factor Xa inhibitors provided improved DVT prophylaxis with lower rates of anaemia compared to enoxaparin and warfarin."*[21] (p. 1)

Main Study Findings	Author's Conclusions
– Enoxaparin: 17% – Warfarin: 15% – Factor Xa inhibitors: 12% Bleeding-related complications at 90 days (No significant difference among the agents, P = 0.94) – Aspirin: 2% – Enoxaparin: 1% – Warfarin: 2% – Factor Xa inhibitors: 1% Compound annual growth rate of utilization from 2007 to 2015 – Aspirin: 33% – Enoxaparin: 7% – Warfarin: -1% – Factor Xa inhibitors: 31%	
Baumgartner et al., 2019[22]	
Aspirin-only vs. anticoagulant-only or combination of anticoagulant and aspirin – after 90 days of TKA or THA *Clinical effectiveness:* VTE (Aspirin-only vs. any anticoagulant) after TKA – Unadjusted OR (95% CI) = 0.69 (0.56 to 0.86); **P = 0.001** – Adjusted OR (95% CI) = 0.70 (0.56 to 0.87); **P = 0.002** VTE (Aspirin-only vs. any anticoagulant) after THA – Unadjusted OR (95% CI) = 0.81 (0.56 to 1.17); P = 0.26 – Adjusted OR (95% CI) = 0.93 (0.62 to 1.38); P = 0.72 *Safety:* After TKA, Unadjusted prosthetic complications in-hospital – Aspirin-only: 0.3% – Anticoagulant-only: 0.1% – Both anticoagulant and aspirin: 0.1% Unadjusted hospital readmission within 30 days due to prosthetic complications – Aspirin-only: 10.1% – Anticoagulant-only: 10.7% – Both anticoagulant and aspirin: 9.4% Unadjusted hospital readmission within 30 days due to DVT – Aspirin-only: 1.0% – Anticoagulant-only: 0.6% – Both anticoagulant and aspirin: 0.4% Unadjusted hospital readmission within 30 days due to PE – Aspirin-only: 2.3% – Anticoagulant-only: 2.1% – Both anticoagulant and aspirin: 2.1% Unadjusted prosthetic complications during outpatient visit within 90 days – Aspirin-only: 1.8% – Anticoagulant-only: 1.3%	*"More than a fourth of all patients received aspirin as the sole antithrombotic agent after knee or hip arthroplasty. Postoperative thromboprophylaxis with aspirin-only was not associated with higher risk of postoperative venous thromboembolism compared with anticoagulants after hip and knee arthroplasty."*[22] (p. 2038)

Main Study Findings	Author's Conclusions
– Both anticoagulant and aspirin: 1.1% After THA, Unadjusted prosthetic complications in-hospital – Aspirin-only: 0.2% – Anticoagulant-only: 0.2% – Both anticoagulant and aspirin: 0.4% Unadjusted hospital readmission within 30 days due to prosthetic complications – Aspirin-only: 16.5% – Anticoagulant-only: 14.8% – Both anticoagulant and aspirin: 20.0% Unadjusted hospital readmission within 30 days due to DVT – Aspirin-only: 2.2% – Anticoagulant-only: 0.6% – Both anticoagulant and aspirin: 0% Unadjusted hospital readmission within 30 days due to PE – Aspirin-only: 2.2% – Anticoagulant-only: 1.0% – Both anticoagulant and aspirin: 0% Unadjusted prosthetic complications during outpatient visit within 90 days – Aspirin-only: 3.3% – Anticoagulant-only: 2.3% – Both anticoagulant and aspirin: 2.3% *Utilization:* – Aspirin-only: 27.9% of all patients – Warfarin: 24.2% – Enoxaparin: 24.1%	
Hood et al., 2019[23]	
Aspirin-only vs. anticoagulant-only – after 90 days of TKA *Clinical effectiveness (a non-inferiority analysis):* Composite endpoint (VTE or death) – Unadjusted OR (95% CI) = 0.82 (0.66 to 1.02); P = 0.07 – Adjusted OR (95% CI) = 0.85 (0.68 to 1.07); P = 0.23; P for inferiority = 0.007 *Safety:* Bleeding event – Unadjusted OR (95% CI) = 0.81 (0.64 to 1.02); P = 0.08 – Adjusted OR (95% CI) = 0.80 (0.63 to 1.00); P = 0.05; P for inferiority < 0.001 *Utilization:* Between April 1, 2013 ad October 31, 2015 – The use of anticoagulation decreased from 87.4% to 47.9% – The use of aspirin only increased from 10.2% to 50.0%	*"In this study of patients undergoing TKA, aspirin was not inferior to other anticoagulants in the postoperative rate of VTE or death. Aspirin alone may provide similar protection from postoperative VTE compared with other anticoagulation treatments."*[23] (p. 65)
McHale et al. 2019[24]	
Aspirin vs. dabigatran (direct thrombin inhibitor) – after 90 days of TKA or THA	*"No significant differences in safety were found comparing*

Main Study Findings	Author's Conclusions
Clinical effectiveness: After THA, – 90-day VTE: 0% vs. 2.2%; P = 0.17 After TKA, – 90-day VTE: 0% vs. 1.6%; P = 0.32 *Safety:* After THA, – 30-day return to the operation room: 2.7% vs. 0.7%; P = 0.23 – 30-day readmission: 3.6% vs. 1.4%; P = 0.41 – 90-day mortality: 0% vs. 0.7%; P = 0.56 After TKA, – 30-day return to the operation room: 3.2% vs. 1.6%; P = 0.38 – 30-day readmission: 6.3% vs. 5.7%; P = 1.0 – 90-day mortality: 0% vs. 1.6%; P = 0.32	*aspirin to dabigatran for VTE prophylaxis for lower limb arthroplasty, which has not been previously reported and represents significant cost saving implications."*[24] (p. 563)
Rondon et al., 2019[25]	
Aspirin vs. non-aspirin anticoagulants (apixaban, clopidogrel, dabigatran, dipyridamole, enoxaparine, fondaparinux, heparin, lepirudin, rivaroxaban, ticlopidine, and warfarin) – after 30 days, 90 days and 1 year of TKA or THA *Safety:* Death at 30 days – 0.1% vs. 0.3% ; P = 0.004 – Adjusted OR (95% CI) = 0.39 (0.17 to 0.86); P = 0.020 – Primary cause of death was cardiac mortality: 0% vs. 0.1%; P = 0.047 – No significant difference between groups in pulmonary-related death (0% vs. 0.02%), sepsis/infections-related death (0.01% vs. 0.02%), or VTE-related death (0% vs. 0.02%) Death at 90 days – 0.2% vs. 0.4% ; P = 0.007 – Adjusted OR (95% CI) = 0.58 (0.32 to 1.04); P = 0.067 – Primary cause of death was cardiac mortality: 0.04% vs. 0.14%; P = 0.026 – No significant difference between groups in pulmonary-related death (0% vs. 0.03%), sepsis/infections-related death (0.02% vs. 0.04%), or VTE-related death (0% vs. 0.02%) Death at 1 year – 0.3% vs. 0.7% ; P < 0.001 – Adjusted OR (95% CI) = 0.51 (0.32 to 0.81); P = 0.004 – Primary cause of death was cardiac mortality: 0.04% vs. 0.20%; P = 0.005 – No significant difference between groups in pulmonary-related death (0% vs. 0.07%), sepsis/infections-related death (0.04% vs. 0.10%), or VTE-related death (0% vs. 0.03%)	*"The present study demonstrate that the use of aspirin as prophylaxis against VTE following TJA may reduce the risk of mortality. Given the numerous options available and permitted by the current guidelines, orthopaedic surgeons should be aware of the potential added benefits of aspirin when selecting a VTE-prophylactic agent."*[25] (p. 504)

Main Study Findings	Author's Conclusions
Runner et al. 2019[26]	
Less aggressive VTE prophylaxis (aspirin and/or sequential compression devices) vs. More aggressive VTE prophylaxis (LMWH [enoxaparin], warfarin, rivaroxaban, fondaparinux, or other strategies) – after 90 days of TKA or THA *Safety:* After TJA (combining TKA and THA), – No complications: 95.5% vs. 93.0%; P < 0.001 – Mild bleeding: 0.4% vs. 1.3%; P < 0.001 – Moderate bleeding: 2.1% vs. 2.7%; P = 0.002 – Severe bleeding: 0.9% vs. 1.2%; P = 0.010 – Mild thrombosis: 0.2% vs. 0.9%; P < 0.001 – Moderate thrombosis: 0.4% vs. 1.2%; P < 0.001 – Severe thrombosis/fatal PE: 0.0% vs. 0.1%; P = 0.016 – Infections: 1.3% vs. 1.9%; P = 0.001 – Death: 0.3% vs. 0.7%; P < 0.001 After TKA, – No complications: 95.7% vs. 92.3%; P < 0.001 – Mild bleeding: 0.4% vs. 1.6%; P < 0.001 – Moderate bleeding: 2.1% vs. 2.7%; P = 0.027 – Severe bleeding: 0.8% vs. 1.3%; P = 0.011 – Mild thrombosis: 0.2% vs. 1.2%; P < 0.001 – Moderate thrombosis: 0.3% vs. 1.5%; P < 0.001 – Severe thrombosis/fatal PE: 0.0% vs. 0.1%; P = 0.053 – Infections: 1.3% vs. 2.0%; P = 0.006 – Death: 0.2% vs. 0.6%; P = 0.002 After THA, – No complications: 95.3% vs. 93.8%; P = 0.001 – Mild bleeding: 0.4% vs. 1.0%; P < 0.001 – Moderate bleeding: 2.1% vs. 2.7%; P = 0.040 – Severe bleeding: 1.0% vs. 1.2%; P = 0.348 – Mild thrombosis: 0.3% vs. 0.6%; P = 0.009 – Moderate thrombosis: 0.5% vs. 0.9%; P = 0.005 – Severe thrombosis/fatal PE: 0.0% vs. 0.0%; P = 0.172 – Infections: 1.3% vs. 1.8%; P = 0.057 – Death: 0.4% vs. 0.9%; P = 0.003	*"It was not possible to ascertain the individual rationale for use of more aggressive VTE prophylaxis strategies; however, more aggressive strategies were associated with higher rates of bleeding and thrombotic complications. Less aggressive strategies were not associated with higher rate of thrombosis."*[26] (p. 729)
Tan et al., 2019[27]	
Aspirin vs. LMWH (enoxaparin) or warfarin – after 90 days of TKA or THA *Clinical effectiveness:* VTE Standard risk of VTE group – Unadjusted OR (95% CI) for warfarin vs. aspirin: 3.87 (2.61 to 5.75); P < 0.001 – Adjusted OR (95% CI) for warfarin vs. aspirin: 3.73 (2.48 to 5.62); P < 0.001 – Unadjusted OR (95% CI) for LMWH vs. aspirin: 9.20 (6.19 to 13.67); P < 0.001 – Adjusted OR (95% CI) for LMWH vs. aspirin: 8.28 (5.55 to 12.35); P < 0.001 High risk of VTE group – Unadjusted OR (95% CI) for warfarin vs. aspirin: 3.47 (2.52 to 4.79); P < 0.001	*"The results of this multi-institutional study demonstrate that the use of warfarin and low-molecular-weight heparin in higher-risk patients does not necessarily result in a reduction in symptomatic venous thromboembolism. Aspirin administered to higher-risk patients seems to be as effective as potent anticoagulation and more*

Main Study Findings	Author's Conclusions
– Adjusted OR (95% CI) for warfarin vs. aspirin: 3.05 (2.08 to 4.47); P < 0.001 – Unadjusted OR (95% CI) for LMWH vs. aspirin: 2.36 (1.76 to 3.17); P < 0.001 – Adjusted OR (95% CI) for LMWH vs. aspirin: 1.95 (1.43 to 2.65); P < 0.001 *Safety:* Periprosthetic joint infections – Aspirin was associated with lower periprosthetic joint infections compared with LMWH or warfarin in all VTE risk groups (P < 0.001) *Utilization:* In high risk of VTE – Aspirin: 30.5% – LMWH: 50.9% – Warfarin: 18.6% In standard risk of VTE – Aspirin: 2.3% – LMWH: 6.8% – Warfarin: 3.5%	*effective than warfarin."*[27] (p. 589)
Yang et al., 2019[28]	
Aspirin vs. DOACs (apixaban, dabigatran, rivaroxaban) – after 90 days of TKA or THA *Clinical effectiveness:* Composite endpoint (VTE or bleeding within 90 days) – Adjusting for propensity scoring: No significantly different between the aspirin and DOACs groups – Unadjusted: 13.3% vs. 12.9%; P = 0.89 VTE – Unadjusted: 1.4% vs. 0.5%; P = 0.62 DVT – Unadjusted: 1.4% vs. 0.5%; P = 0.62 PE – Unadjusted: 0.5% vs. 0%; P = 1 *Safety (unadjusted):* Any bleeding: 12.9% vs. 12.4%; P = 0.88 Major bleeding: 1% vs. 1%; P = 1 Clinically overt bleeding: 3.8% vs. 4.3%; P = 0.8 Transfusion with at least 2 units of blood: 2.9% vs. 7.1%; P = 0.04 Readmission due to bleeding or VTE events: 1.9% vs. 1.9%; P = 1 Readmission die to VTE: 0% vs. 0.5%; P = 0.3 Readmission due to bleeding: 1.9% vs. 1.9%; P = 1	*"No difference in net clinical outcome was observed in patients who received a DOAC or aspirin for VTE prophylaxis after major orthopedic surgery."*[28] (p. S55)
Yuenyongviwat et al., 2019[29]	
Aspirin vs. rivaroxaban – after 48 hours of TKA	*"Aspirin and rivaroxaban were effective and safe as VTE*

Main Study Findings	Author's Conclusions
Clinical effectiveness: DVT or PE – No incidence in both groups *Safety:* Total closed suction drainage output – 490 mL (IQR 372.5 to 600) vs. 540 (IQR 410 to 695); P = 0.10 Blood transfusion – 19% vs. 25%; P = 0.37 Bleeding-related complications – No incidence in both groups	*chemoprophylaxis in total knee arthroplasty."*[29] (p. 877)
Goel et al., 2018[30]	
Aspirin vs. warfarin – after 90 days SBTKA *Clinical effectiveness:* PE – Unadjusted: 1.05% (95% CI 0.65 to 1.70) vs. 2.32% (1.76 to 3.05) – Adjusted: 1.0% (0.86 to 1.2) vs. 2.2% (2.0 to 2.4%) – Adjusted RR (95% CI): 0.44 (0.25 to 0.78); P = 0.005 VTE (DVT and PE) – Unadjusted: 1.57% (95% CI 1.06 to 2.33) vs. 2.50% (1.92 to 3.25) – Adjusted: 1.5% (95% CI 1.3 to 1.7) vs. 2.3% (95% CI 2.1 to 2.6%) – Adjusted RR (95% CI): 0.62 (0.38 to 1.01); P = 0.052 Comparison between SBTKA and UTKA – The risk of PE was 204% higher for patients undergoing SBTKA compared to those undergoing UTKA	*"Aspirin is more effective than warfarin for the prevention of VTE following SBTKA, and serves as the more appropriate agent for VTE prophylaxis for patients in all risk categories. Furthermore, patients undergoing SBTKA are at a substantial increased risk of VTE, even more so for those with significant underlying risk Factors. Patients should be informed about the risks associated with undergoing SBTKA."*[30] (p. 68)
Bonutti et al., 2017[31]	
Aspirin and fish oil vs. aspirin and mechanical pulsatile stocking vs. rivaroxaban – after 90 days of TKA *Clinical effectiveness:* DVT – Aspirin and fish oil: 0.33% – Aspirin and mechanical pulsatile stocking: 7% – Rivaroxaban: 1% – OR (95% CI) for aspirin and fish oil vs. aspirin and mechanical pulsatile stocking: 0.045 (0.006 to 0.339; P < 0.05) – OR (95% CI) for aspirin and fish oil vs. rivaroxaban: 0.416 (0.038 to 4.622; P > 0.05) PE – No PE events reported in any cohort. *Safety:*	*"This study demonstrated the potentially synergistic anti0thromboembolic effect in aspirin and fish oil in the prevention of post-operative venous thromboembolism in primary TKA patients. Based on the results from this study, the authors conclude that the combination of aspirin and fish oil maybe an excellent thromboprophylactic modality for patients to use after TKA. These results warrant further, larger prospective studies analyzing the use of fish oil supplements in VTE prophylaxis."*[31] (p. 1)

Main Study Findings	Author's Conclusions
Bleeding complications – Aspirin and fish oil: 0.33% – Rivaroxaban: 12% – OR (95% CI) for aspirin and fish oil vs. rivaroxaban: 0.028 (0.004 to 0.210; P < 0.050)	
Chu et al., 2017[32]	
Aspirin vs. anticoagulant or anticoagulant plus aspirin (anticoagulants: warfarin, injectable heparin, LMWH (enoxaparin, dalteparin, or tinzaparin), fondaparinux, or DOACs (dabigatran, rivaroxaban or apixaban) – after 30 days of TKA or THA *Clinical effectiveness:* VTE – For TKA: adjusted OR (95% CI) = 0.34 (0.24 to 0.48) – For THA: adjusted OR (95% CI) = 0.82 (0.45 to 1.51)	*"Aspirin was uncommonly administered as the sole prophylactic agent after hip or knee arthroplasty in this study. However, patients who received aspirin-only had similar rates of post-operative VTE compared to patients who received anticoagulants. Further research should focus on distinguishing which patients benefit more from anticoagulants versus aspirin after arthroplasty."*[32] (p. 65)

CI = confidence interval; DOAC = direct oral anticoagulant; THA = total hip arthroplasty; TJA = total joint arthroplasty; TKA = total knee arthroplasty; TOST = two one-side tests; OR = odds ratio; SBTKA = simultaneous bilateral TKA; SCD = sequential compression device; UTKA = unilateral TKA; vs. = versus.

Table 11: Summary of Recommendations of Included Guidelines

Recommendations
ASH, Anderson et al., 2019[33]
"Question: Should ASA vs anticoagulants be used for patients undergoing total hip or knee arthroplasty? • *For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel suggests using ASA or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects)."*[33] (p. 3911)
NICE, 2019[34]
"Offer VTE prophylaxis to people undergoing elective hip replacement surgery whose risk of VTE outweighs their risk of bleeding. *Choose any one of:* • *LMWH for 10 days followed by aspirin (75 or 150 mg) for a further 28 days* • *LMWH for 28 days combined with anti-embolism stockings (until discharge)* • *Rivaroxaban"*[34] (p. 148, 149) *"Offer VTE prophylaxis to people undergoing elective knee replacement surgery whose VTE risk outweighs their risk of bleeding.* *Choose any one of:* • *Aspirin (75 or 150 mg) for 14 days* • *LMWH for 14 days combined with anti-embolism stockings until discharge* • *Rivaroxaban"*[34] (p. 224)
ESA VTE Guidelines Task Force, Jenny et al., 2018[35]
• *"We recommend the use of aspirin as an option for venous thromboembolism (VTE) prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (Grade 1B)."*[35] (p. 128) • *"We suggest the use of aspirin for VTE prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery (high-risk procedures) in patients without high VTE risk (Grade 2C)."*[35] (p. 128).

Recommendations

- *"We suggest the use of aspirin for VTE prevention after low-risk orthopaedic procedures in patients with a high VTE risk or other high-risk orthopaedic procedures in patients without a high VTE risk (Grade 2C)."*[35] (p. 128)
- *"We suggest the use of aspirin for VTE prevention after total hip arthroplasty, total knee arthroplasty and hip fracture surgery in patients with an increased bleeding risk (Grade 2C)."*[35] (p. 128)

ASA = aspirin; ASH = American Society of Hematology; ESA = European Society of Anesthesiology; LMWH = low molecular weight heparin; VTE = venous thromboembolism.

Table 12: High-Level Summary of Findings by Comparison and Outcome in SRs

Overarching category	Intervention vs. Comparator	Population	Direction of Effect by Outcome						
			Effectiveness			Safety			
			VTE	DVT	PE	Death	Bleeding	Wound infections/complications	Readmission
Aspirin vs. LMWH	Aspirin vs. enoxaparin or dalteparin[13,14,17]	THA or TKA	↔; ↔	↔; ↔; ↔	↔; ↔; ↔	–	↔; ↔	↔	–
Aspirin vs. Factor Xa inhibitors	Aspirin vs. rivaroxaban[14,15]	THA or TKA	↔; ↔	↔; ↔	↔	–	↔	↔	↔
Aspirin vs. Another anticoagulant	Aspirin vs. [a]anticoagulant[14]	THA or TKA	↔	↔	↔	–	↔	↔	–
	Aspirin vs. [b]anticoagulant[16]	THA or TKA	↔	–	–	↔	↔	–	–

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

Note. ↑ suggests intervention more favourable than comparator; ↓ suggests intervention less favourable than comparator; ↔ suggests not statistically significant; [?] suggests not compared statistically or non-interpretable; – suggests not measured.

[a] Rivaroxaban, LMWH (enoxaparin, dalteparin), low molecular weight dextran, heparin, or warfarin

[b] Rivaroxaban, warfarin, heparin, or placebo

Table 13: High-Level Summary of Findings by Comparison and Outcome in Primary Studies

Overarching category	Intervention vs. Comparator	Population	Direction of Effect by Outcome						
			Effectiveness			Safety			
			VTE	DVT	PE	Death	Bleeding	Wound infections/ complications	Readmission
Aspirin vs. LMWH	Aspirin vs. enoxaparin[19,27]	THA or TKA	↔; ↑	–	–	–	–	↑	–
Aspirin vs. Factor Xa inhibitors	Aspirin vs. rivaroxaban[18]	THA	↓	↔	↓	↔	↔	↔	↓
		TKA	↓	↔	↓	↔	↔	↔	↓
	Extended aspirin vs. modified rivaroxaban[19]	THA or TKA	↔	–	–	–	–	–	–
	Aspirin vs. rivaroxaban[29]	TKA	–	No events	No events	–	No events	–	–
	Aspirin + fish oil vs. rivaroxaban[31]	TKA	–	↔	No events	–	↑	–	–

Overarching category	Intervention vs. Comparator	Population	Direction of Effect by Outcome						
			Effectiveness			Safety			
			VTE	DVT	PE	Death	Bleeding	Wound infections/ complications	Readmission
Aspirin vs. Direct thrombin inhibitors	Aspirin vs dabigatran[18,24]	THA	↓; ↔	↓	↓	↔; ↔	↔	↔	↔; ↔
		TKA	↓/↔	↔	↔	↔; ↔	↔	↔	↔; ↔
Aspirin vs. Warfarin	Aspirin vs. warfarin[20,27]	THA or TKA	↔; ↑	–	–	↔	↔	↑; ↑	↔
	Aspirin vs. warfarin[30]	TKA	[?]	–	↑	–	–	–	–
Aspirin vs. Another anticoagulant	Aspirin vs. [a]another anticoagulant[21]	THA	–	↑ vs. enoxaparin, warfarin ↔ vs. Factor Xa inhibitors	[?]	–	↔	–	–
	Aspirin vs. [b]another anticoagulant[22]	THA	↔	–	–	–	–	[?]	[?]
		TKA	↑	–	–	–	–	[?]	[?]
	Aspirin vs. [c]another anticoagulant[23]	TKA	↔ for composite of VTE or death	–	–	–	↔	–	–
	Aspirin vs. [d]another anticoagulant[25]	THA or TKA	–	–	–	↑	–	–	–
	Aspirin vs. [e]another anticoagulant[26]	THA or TKA	–	–	–	↑	↑	↑	–
	Aspirin vs. [f]another anticoagulant[28]	THA or TKA	↔	↔	↔	–	↔	–	↔

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

Note. ↑ suggests intervention more favourable than comparator; ↓ suggests intervention less favourable than comparator; ↔ suggests not statistically significant; [?] suggests not compared statistically or non-interpretable; – suggests not measured.

[a] Enoxaparin, warfarin, or Factor Xa inhibitors

[b] Heparin, LMWH, fondaparinux, warfarin, Factor Xa inhibitors

[c] Factor Xa inhibitors, direct thrombin inhibitors, LMWH, synthetic pentasaccharides, or warfarin

[d] apixaban, clopidogrel, dabigatran, dipyridamole, enoxaparine, fondaparinux, heparin, lepirudin, rivaroxaban, ticlopidine, or warfarin

[e] LMWH, warfarin, rivaroxaban, fondaparinux, or other strategies

[f] Apixaban, dabigatran, or rivaroxaban