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Clinical effectiveness and safety of aspirin and other anticoagulants for venous thromboembolism prophylaxis after major orthopedic surgery: a systematic review and meta-analysis of randomized clinical trials

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- *Purpose:* Patients undergoing major orthopedic surgeries, such as total hip replacement (THR), total knee replacement (TKR), and trauma surgery, are at an elevated risk of venous thromboembolism (VTE), causing significant morbidity and mortality. Previous studies have investigated aspirin as a thromboprophylactic agent for arthroplasty, besides trauma surgery. Therefore, we sought to analyze the efficacy of aspirin compared to that of other anticoagulants for VTE prophylaxis in patients undergoing major orthopedic surgeries.
- *Methods:* This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered with the PROSPERO register. Randomized controlled trials that investigated the use of aspirin for thromboprophylaxis in major orthopedic lower limb surgeries were included and analyzed. Quality analysis of the literature and level of evidence were assessed. The primary clinical outcome was VTE. Secondary clinical outcomes included mortality, bleeding events, and wound complications.
- *Results:* Eight high-quality studies with level 2 evidence (published within 2006–2021) were included, comprising 6220 patients. The incidence of VTE with aspirin was not found to be more significant than other anticoagulants (risk ratio (RR) = 1.18, 95% CI: 0.89–1.58, $P = 0.25$). Regarding secondary outcomes, there were no significant differences between aspirin and other anticoagulants (mortality (RR = 1.40, 95% CI: 0.27–7.23, $P = 0.69$), bleeding events (RR = 0.89, 95% CI: 0.57–1.39, $P = 0.61$), or wound complications (RR = 0.64, 95% CI: 0.30–1.35, $P = 0.24$)).
- *Conclusion:* The current meta-analysis did not show any difference between aspirin and other anticoagulants as thromboprophylactic agents in preventing VTE in patients who underwent major orthopedic surgeries.

Keywords

- thromboprophylaxis
- aspirin
- anticoagulants
- arthroplasty
- major orthopedic surgery

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Introduction

Patients undergoing major orthopedic surgeries, such as total hip replacement (THR), total knee replacement (TKR), and trauma surgery (hip/femur fracture), are at an elevated risk of venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most common forms of VTE incidence, causing significant morbidity and mortality (1). VTE in major orthopedic surgery is caused by several prothrombotic mechanisms, such as vein injury, coagulation activation due to bone and tissue injury, heat from cement polymerization, and prolonged immobilization (2, 3). Recent studies from 363 530 patients showed an overall incidence of VTE in patients

who underwent THR and TKR as 0.6 and 1.4%, respectively (4). It accounts for 1 in 167 patients undergoing THR and 1 in 71 patients undergoing TKR (4). The incidence of DVT is also quite similar in patients undergoing orthopedic trauma surgery, accounting for 0.84% (5).

Several guidelines have been proposed to prevent VTE following major orthopedic surgeries. American Academy of Orthopedic Surgeons suggested that patients who undergo THR or TKR should be given prophylaxis for VTE (6). National Institute for Health and Care Excellence guidelines in 2018 recommended giving low-molecular-weight heparin (LMWH) followed by aspirin or LMWH combined with stockings in patients undergoing THR. Meanwhile, the recommendation for patients undergoing TKR was aspirin or LMWH (7). The American College of Chest Physicians in 2012 recommended the administration of LMWH, unfractionated heparin, novel oral anticoagulant, and aspirin for VTE prophylaxis (8). The Scottish Intercollegiate Guidelines Network recommended the use of several notable anticoagulants but not the use of aspirin as a single pharmacological agent for VTE prophylaxis (9).

Previous studies and meta-analyses have investigated aspirin as a thromboprophylactic agent for arthroplasty apart from trauma surgery (10, 11). Therefore, we sought to analyze the efficacy of aspirin compared to that of other anticoagulants (LMWH and factor Xa inhibitors) for VTE prophylaxis in patients undergoing major orthopedic surgeries, including trauma patients (1, 12).

Methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). The study protocol was registered with PROSPERO (ID: CRD42022299742). The patient, intervention, comparison, outcome (PICO) of this study was P: lower limb arthroplasty and trauma; I: aspirin; C: other anticoagulants; and O: incidence of venous thromboembolism.

Search strategy

A thorough literature search was performed on PubMed, Medline (via EBSCO), ProQuest, and ScienceDirect in February 2022 with the following search string after consulting two librarians, which consisted of 'aspirin', 'thromboembolism', 'arthroplasty', and 'orthopedics'. The search in PubMed was conducted using the specific strings: (('aspirin'[MeSH Terms] OR 'aspirin'[All Fields] OR 'aspirins'[All Fields] OR 'aspirin s'[All Fields] OR 'aspirine'[All Fields]) AND ('thromboembolic'[All Fields] OR 'thromboembolism'[MeSH Terms] OR 'thromboembolism'[All Fields] OR 'thromboembolisms'[All Fields] OR 'thromboembolization'[All Fields]) AND ('orthopaedic'[All Fields] OR 'orthopedics'[MeSH Terms] OR 'orthopedics'[All Fields] OR 'orthopedic'[All Fields] OR 'orthopaedical'[All Fields] OR 'orthopedical'[All Fields] OR 'orthopaedics'[All Fields] OR ('arthroplasty'[MeSH Terms] OR 'arthroplasty'[All Fields] OR 'arthroplasties'[All Fields]))).

Study selection

All included studies were randomized controlled trials (RCTs) published in English between 2002 and 2022. Studies comparing aspirin to other anticoagulants as thromboprophylactic agents in major orthopedic lower limb surgery, with a minimum follow-up period of 4 weeks, were included. Major orthopedic surgeries included total knee arthroplasty (TKA), total hip arthroplasty (THA), and trauma surgery. Studies before 2002 that were not in English, animal studies, and studies with a sample size less than 50 patients were excluded.

Quality appraisal and risk of bias assessment

Two independent authors (LCS and RHS) performed identification, selection, data extraction, and quality assessment. Differences in opinions between the two reviewers were resolved by reassessment and discussion with the third author (EK). The quality of the literature was assessed using the Jadad Scale (which consists of randomization, masking, withdrawal, and accountability of all patients). To evaluate the risk of bias, the reviewers rated each of the five items from the scale into dichotomous variables. The overall score was calculated by adding all item scores. A score was given to every paper to classify them as low- or high-quality studies. The level of evidence was assessed using the Oxford Center for Evidence-Based Medicine Guideline 2011 (14).

Data extraction and analysis

All data were extracted from the text, figures, tables, and associated supplementary files of each included study. These data included (i) article (year of publication) and demographic characteristics (sample size, gender, age, and history of VTE); (ii) follow-up duration; (iii) type of surgery; (iv) type, dosage, and duration of thromboprophylaxis; (v) day of mobilization; and (vi) clinical outcomes. The primary clinical outcome was VTE (DVT or PE). Secondary clinical outcomes included mortality, bleeding events, and wound complications (until the last follow-up). The clinical outcomes of patients using aspirin as a thromboprophylactic agent were compared to those with other agents.

The Review Manager (RevMan version 5.4; Cochrane Collaboration, Oxford, United Kingdom) software was used for statistical analysis using the Mantel–Haenszel method. A subgroup analysis was performed for the elective and trauma groups. A dichotomous variable and

risk ratio (RR) with a 95% CI were used to measure the effect. Heterogeneity between the studies was identified using the I^2 value. Data were also plotted using forest plots to determine the outcomes. A funnel plot was also used to assess publication bias.

Results

Study selection

A total of 568 studies were retrieved during the initial screening (Fig. 1).

A total of 558 studies were excluded after reviewing titles, abstracts, and duplications. Of the remaining ten studies, one study was excluded because aspirin was not compared with other anticoagulants (15), and another study used aspirin with other agents in the intervention group (16).

Study quality assessment

The level of evidence was assessed using the Oxford Center for Evidence-Based Medicine Guideline 2011, which found that all eight studies had level 2 evidence (14). According to the quality assessment, all studies were categorized as high-quality studies (Table 1).

Article and demographic characteristics

The characteristics of the eight studies included in our study are shown in Table 2.

In total, 6220 patients were included in the current study. The studies were published between 2006 and 2021, with a sample size of 70–3424 patients. The number of studies that discussed THA, TKA, and trauma surgeries was 3, 5, and 1, respectively.

Primary outcomes

Eight studies (17, 18, 19, 20, 21, 22, 23, 24) evaluated VTE following major orthopedic surgery. There was no significant difference in VTE (Fig. 2) following major orthopedic surgery between aspirin and other anticoagulants (RR = 1.18, 95% CI: 0.89–1.58, $P = 0.25$). Heterogeneity was not observed ($I^2 = 0\%$).

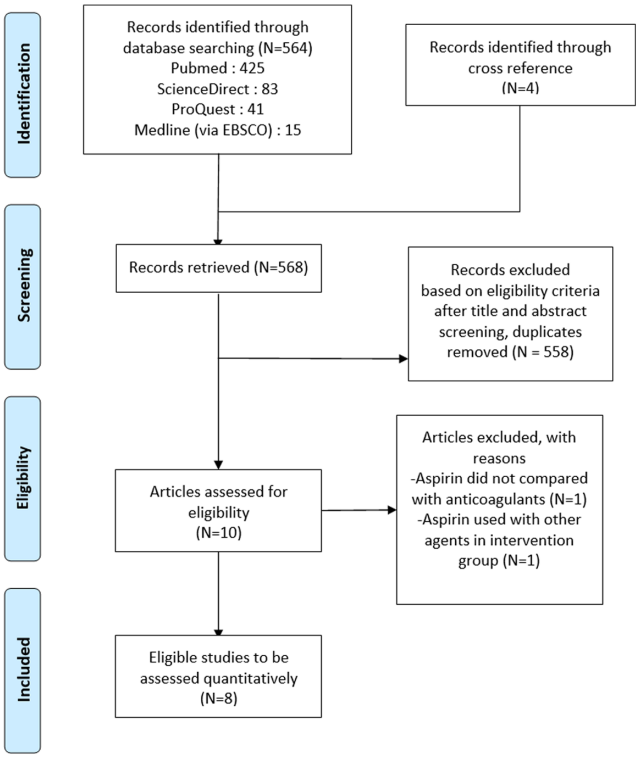

Figure 1
PRISMA flow chart.

In the subgroup analysis, seven studies evaluated VTE following elective surgery (Fig. 3) (17, 19, 20, 21, 22, 23, 24). There was no significant difference in VTE following major orthopedic surgery between aspirin and other anticoagulants (RR = 1.19, 95% CI, 0.86–1.67 $P = 0.30$). A low heterogeneity was observed ($I^2 = 9\%$). One study evaluated VTE following trauma surgery and found it in 10 of 165 patients in the aspirin group and 10 of 164 patients in the LMWH group (18).

Secondary outcomes (mortality, bleeding events, and wound complications)

The secondary outcomes were mortality, bleeding events, and wound complications. The use of aspirin did not show a significant difference in mortality compared to that

Table 1 Study quality assessment with Jadad scale.

Criteria	Reference							
	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)
Was the study described as random?	1	1	1	1	1	1	1	1
Was the randomization scheme described and appropriate?	1	1	1	1	1	1	1	1
Was the study described as double blind?	0	0	1	0	0	1	1	0
Was the method of double blinding* appropriate?	0	0	1	0	0	1	0	0
Was there a description of dropouts and withdrawal?	1	1	1	1	1	1	0	1
Total score†	3	3	5	3	3	5	3	3

*The patient and assessor appropriately blinded; †Jadad Scale, score quality: 0–2 (low); 3–5 (high).

Table 2 Summary of characteristics of included studies.

Reference	Patients, *n*	Gender (M:F)	Mean age	History of VTE	Follow-up	Surgery	Treatment	Mobilization after surgery (days)	Outcome
(17)	70	24:46	52.2	None	At POD 14 and POD 30	THA	Aspirin 100 mg bid: 34 patients (5 weeks); Rivaroxaban 10 mg qd: 36 patients (5 weeks)	POD1 (walk with crutch assisted)	Evaluation with lower limb USG, 3 patients in both groups with distal DVT.
(18)	329	223:106	47	15	For 90 days	Trauma[1]	Aspirin 81 mg bid: 165 patients*; Enoxaparin 30 mg bid : 164 patients*	Not stated	90 days event-free in 99 patients in the aspirin group (59.9%) and 98 patients in the LMWH group (59.4%); No significant statistic difference within both group
(19)	3424	1637:1787	62.8	81	For 90 days	THA and TKA	Aspirin : 81 mg qd: Hip : 902 patients (30 days), Knee : 805 patients (9 days); Rivaroxaban : 10 mg qd: Hip :902 patients (30 days); Rivaroxaban : 10 mg qd : 815 patients (9 days)	Not stated	VTE occurred in 11 patients (0.64%) among aspirin group and 12 patients (0.70%) in rivaroxaban group ($P < 0.001$ for noninferiority and $P = 0.84$ for superiority).
(20)	120	9:111	64.4	None	For 6 weeks	TKA	Aspirin 100 mg qd : 60 patients (14 days); LMWH 5000 U/day, POD 1-5, continued with Rivaroxaban 10 mg qd (POD 6 -14)	POD1 (active-passive motion, walking with crane)	DVT in 10 patients (16.7%) when using Aspirin and 11 patients (18.3%) when using LMWH and rivaroxaban but no significant difference ($P = 0.500$)
(21)	324	80:244	64	None	For 4 weeks	TKA	Aspirin 100 mg qd : 110 patients (14 days); Rivaroxaban 10 mg qd : 102 patients (14 days); LMWH 4000 U qd : 112 patients (14 days)	POD 2 (walking with walking aids under the guidance of caregivers)	Incidence of DVT higher in Aspirin group versus Rivaroxaban (18 (16.36%) vs 3 (2.94%),$P = 0.017$)); No significant difference in DVT incidence with Aspirin compared to s.c. LMWH (14 (12.50%) vs 18 (16.36%), $P = 0.831$).
(22)	778	444:334	57.8	13	For 90 days	THA	Aspirin 81 mg qd : 380 patients (28 days); Dalteparin 5000 U qd : 398 patients (28 days)	Not stated	Venous thromboembolism was found in 5 of 398 patients among Dalteparin group and 1 of 380 patients among Aspirin group. Aspirin was found to be significantly non-inferior ($P < 0.001$) but not superior ($P = 0.22$) to Dalteparin.
(23)	900	328:572	63.8	Not stated	For 12 months	TKA	Aspirin 325 mg bid: 194 patients (4 weeks); Enoxaparin 40mg qd SC (2 weeks)+Aspirin 325 mg bid (2 weeks): 706 patients	POD 1	Symptomatic DVT occurs in 4 patients (2.1%) within the aspirin group and 15 (2.1%) within the LMWH group ($P = 0.957$).
(24)	275	99:176	68.9	None	For 4–-6weeks	TKA	Aspirin 325 mg bid+CCD: 129 (4 weeks); Enoxaparin 30mg bid (until discharge), 40mg qd (3 weeks)+ CCD : 135	Not stated.	The incidence of DVT for Aspirin (18/129) and Enoxaparin (17/135) was without significant difference ($P = 0.34$).

[1]Extremity fracture proximal to the carpals or metatarsal, and hip or acetabular fracture;
*Duration depends on hospital guideline.
CCD, calf compression device; THA, total hip arthroplasty; TKA, total knee arthroplasty,

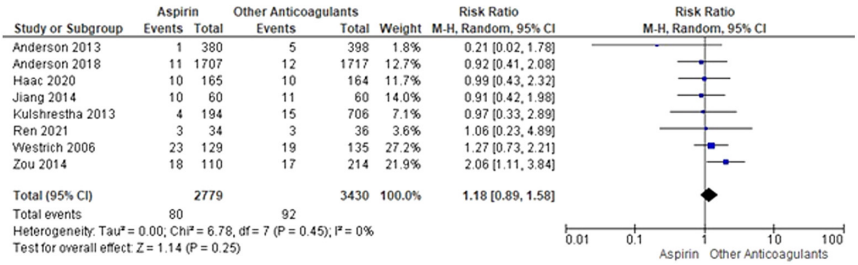

Figure 2
Forest plot of VTE.

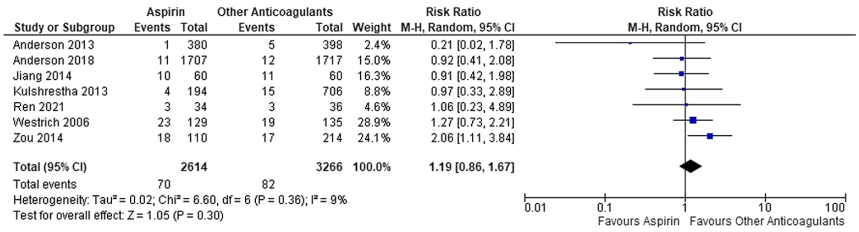

Figure 3
Forest plot of VTE in elective group.

with other anticoagulants (RR = 1.40, 95% CI: 0.27–7.23, *P* = 0.69) (Fig. 4).

Among elective surgeries, the use of aspirin also showed no significant difference in mortality when compared to that with other anticoagulants (RR = 1.02, 95% CI: 0.11–9.81, *P* = 0.99) (Fig. 5) (17, 19, 20, 21, 22, 23, 24). In trauma surgery, mortality occurred in 2 of the 165 patients in the aspirin group and in 1 of the 164 patients in the LMWH group (18).

Bleeding events, defined as major bleeding (fatal/symptomatic), >2 g/dL drop in hemoglobin, requiring transfusion, or minor bleeding, following major orthopedic surgery were not significantly different between aspirin and other anticoagulants (RR = 0.89, 95% CI: 0.57–1.39, *P* = 0.61) (Fig. 6).

The subgroup analysis of elective surgery also reported the same result (RR = 0.81, 95% CI: 0.34–1.91, *P* = 0.63) (Fig. 7) (17, 19, 20, 21, 22, 23, 24). Among

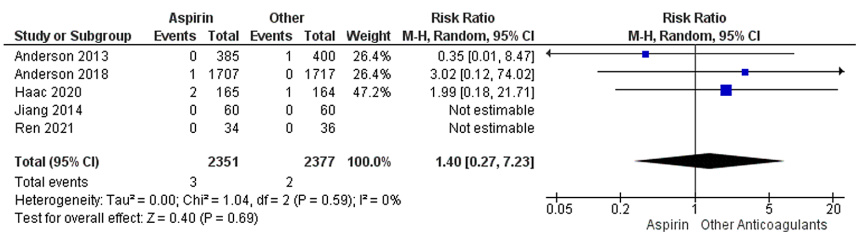

Figure 4
Forest plot of mortality.

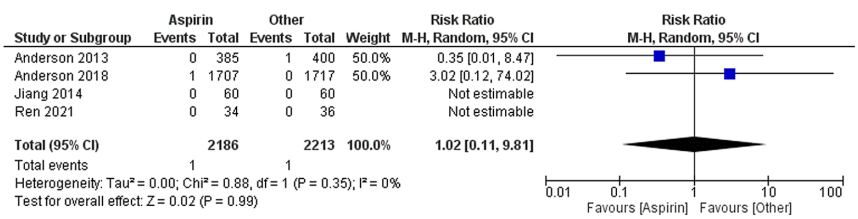

Figure 5
Forest plot of mortality in elective group.

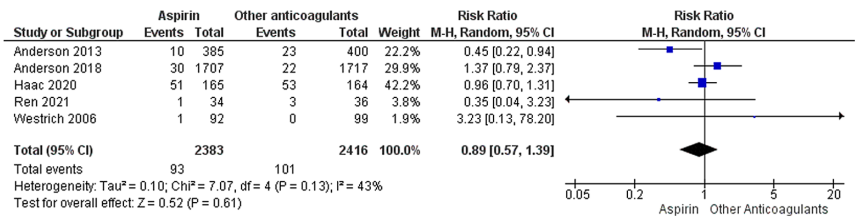

Figure 6
Forest plot of bleeding events.

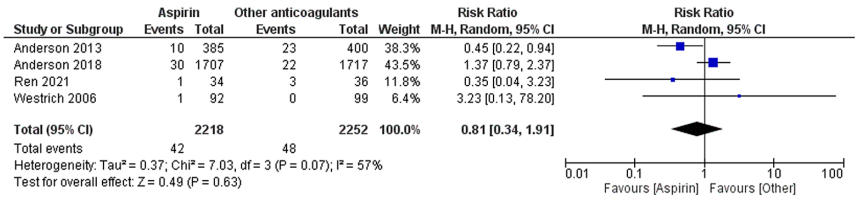

Figure 7
Forest plot of bleeding events in elective group.

trauma surgeries, mortality occurred in 51 of 165 patients in the aspirin group and 53 of 164 patients in the LMWH group (18).

The wound complications (wound effusion, deep surgical infection, or superficial wound infection) were also not significantly different between patients treated with aspirin and other anticoagulants following major orthopedic surgery (RR = 0.64, 95% CI: 0.30–1.35, $P = 0.24$) (Fig. 8). No drainage use was reported.

Furthermore, the wound complications in the subgroup analysis of elective surgery also showed no significant difference (RR = 0.57, 95% CI: 0.19–1.75, $P = 0.33$) (Fig. 9) (17, 19, 20, 21, 22, 23, 24). Haac *et al.* reported that 12 of 165 patients in the aspirin group and 15 of 164 patients in the LMWH group had wound complications after trauma surgery (18).

Discussion

The current study found no significant difference between aspirin and other anticoagulants in reducing VTE events in patients who underwent a major orthopedic surgery. There were also no significant differences in reducing mortality, bleeding events, and wound complications between aspirin and other anticoagulants.

Previous studies have also supported the findings of the current study. A meta-analysis by Drescher *et al.* in 2014 showed no significant difference between aspirin and other anticoagulants regarding the incidence and the risk of developing DVT after hip fracture surgery and lower extremity arthroplasty (25). Other previous meta-analyses regarding lower extremity arthroplasty also presented results consistent with our study, which showed that aspirin was a safe and effective drug of choice for VTE prophylaxis for TKA and THA. The studies found no significant difference in the efficacy by the use of aspirin for thromboprophylaxis compared to that with other anticoagulants (10, 11). The role of aspirin as the primary VTE prophylaxis was also studied by Sahebally *et al.* who reported that aspirin was effective in orthopedic surgery patients with a high bleeding risk (26).

A non-inferiority analysis of a retrospective cohort of patients undergoing TKA in 29 hospitals in Michigan found that aspirin was not inferior to other anticoagulants in preventing thromboembolic incidence. The study included 41 537 patients and revealed that VTE events occurred in 1.16, 1.42, and 1.31% of patients who used aspirin, other anticoagulants (e.g. LMWH, warfarin, and Xa-inhibitor), and both, respectively. The incidence of VTE was higher (4.79%) in patients who received thromboprophylaxis than in those who did not receive it. This study also suggested that aspirin may be used as a single thromboprophylactic agent (27). A multicenter thromboprophylactic study from more than 600 hospitals in the United States found that aspirin had a lower risk of VTE after TKA than observed by anticoagulant-only or a combination of aspirin and anticoagulation. Among the 231 780 patients who underwent TKA and 110 621 patients who underwent THA, aspirin was not associated

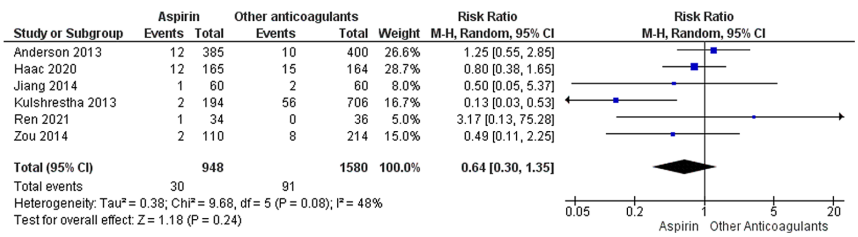

Figure 8
Forest plot of wound complications.

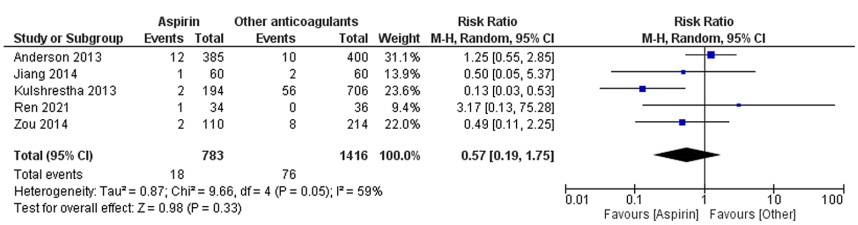

Figure 9
Forest plot of wound complications in elective group.

with a higher risk of VTE in patients who underwent TKA and THA (28).

Regarding secondary outcomes, our mortality, bleeding events, and wound complication results were similar to those reported by previous studies, which found no significant differences between aspirin and other anticoagulants (10, 11, 15, 18, 29, 30). Furthermore, Yhim *et al.*, in a population-based epidemiological study of 306 912 cases (261 260 TKA and 45 652 THA), found that patients who had aspirin as an thromboprophylactic agent had no increased risk for blood transfusion when compared with other anticoagulants (LMWH odds ratio, OR = 1.6 (1.56–1.65), rivaroxaban OR = 1.46 (1.42–1.50), and fondaparinux OR = 1.25 (1.18–1.33)) (29).

In addition to its effectiveness in preventing thromboembolic incidence, aspirin costs less than other anticoagulants. A cost-utility study by Dawoud *et al.* in 2018 found that the cost of single aspirin was the lowest among other thromboprophylactic options. Single aspirin prophylaxis in THR and TKR costs £0.2 to £0.5, whereas others can cost up to £419 (31). Based on these and the results of the current study, aspirin is effective in terms of cost and thromboprophylaxis compared to other anticoagulants.

Although many studies have concluded that aspirin has similar efficacy and safety as other anticoagulants for VTE prophylaxis in major orthopedic surgery patients, a large comparative study showed a different finding, in which patients who underwent TKA benefited more from the use of other anticoagulants (LMWH, factor Xa inhibitors, and fondaparinux) than aspirin. However, this study only included primary TKR patients (32).

Strength and limitations

The strength of this study was the comprehensive literature search of four large databases. The study design included an RCT. The current study only included articles published in the last 20 years to limit variability in cementing techniques. The limitations of this study include the various dosages and lengths of aspirin and comparator administration between studies, the difference in follow-up duration, and the lack of studies on trauma patients. CIs for mortality, bleeding, and wound complication analyses are extensive which also increases the risk of biased observations and conclusions.

Furthermore, a small number of studies related to aspirin as a thromboprophylactic agent in trauma patients have found that there is still a need for further studies on thromboprophylaxis in trauma patients. A Cochrane database review of 16 studies and 3005 patients found that thromboprophylaxis reduced the incidence of DVTs in trauma patients but did not lower the incidence of PE or mortality rates. The results gave us more insight regarding the need for thromboprophylaxis in trauma patients even though the strength of evidence was not high (33). The ongoing PREVENT CLOT trial might present more robust data regarding the effectiveness and safety of aspirin compared to that of other anticoagulants as thromboprophylactic agents among trauma patients (34).

Conclusion

The current meta-analysis showed no difference between aspirin and other anticoagulants as thromboprophylactic agents in preventing VTE in patients who underwent major orthopedic surgeries.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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