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Aspirin versus low-molecular-weight heparin for thromboprophylaxis after orthopaedic surgery: a systematic review and meta-analysis

Haichao Wu, Long Zhou, Qiang Wang, Tao Wang and Siyuan Liang

The article aimed to compare the efficiency and safety of aspirin with low-molecular-weight heparin (LMWH) for thromboprophylaxis in orthopaedic surgery patients. According to the inclusion and exclusion criteria, PubMed, Embase and Cochrane Library database were searched for studies comparing aspirin and LMWH in venous thromboembolism (VTE) prophylaxis until 25 April 2023. The outcome measures included deep venous thrombosis(DVT)/Pulmonary embolism(PE) events, major bleeding events, wound complications, wound infection and death. Six studies met the requirements of our meta-analysis, including 12 470 patients in the aspirin group and 10 857 patients in the LMWH group. The meta-analysis showed that results showed that LMWH was superior to aspirin in preventing VTE events (odds ratio (OR) 1.44, 95% CI 1.24–1.68, $P<0.00001$), whereas there was no significant difference between them in bleeding events (OR 0.95, 95% CI 0.86–1.05, $P=0.33$), wound complication (OR 0.58, 95% CI 0.28–1.17, $P=0.13$), wound infection (OR 1.12, 95% CI 0.86–1.47, $P=0.39$) and mortality (OR 1.04, 95% CI 0.70–1.55, $P=0.83$). In addition, subgroup analysis showed that compared with aspirin, LMWH was more likely to reduce the incidence of DVT events in orthopaedic surgery patients (OR 1.59, 95% CI 1.33–1.91, $P<0.00001$), whereas there was no advantage in reducing the incidence of PE events (OR 1.22, 95% CI 0.62–2.40, $P=0.56$). Despite the similar safety profiles, this meta-analysis showed that LMWH was significantly superior to aspirin in thromboprophylaxis after orthopaedic surgery. LMWH was still the first-line drug for thrombosis prevention in patients who underwent major orthopaedic surgeries. *Blood Coagul Fibrinolysis* **35:187–195 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Venous thromboembolism (VTE) is a complication with a high incidence after major orthopaedic surgeries such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), and is also an important cause of perioperative death and in-hospital unintended death [1]. In the absence of thrombosis prevention, the incidence of deep vein thrombosis after THA and TKA can be as high as 42–57 and 40–80%, respectively, and the risk of fatal PE is 0.1–2 and 0.2–0.7%, so the occurrence of VTE after orthopaedic surgery should be taken seriously [2–4].

The American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) guidelines also state that if not contraindicated, pharmacologic or physical methods should be used to prevent VTE after orthopaedic arthroplasty [5,6]. Low-molecular-weight heparin (LMWH), which acts by enhancing the affinity of antithrombin-III to thrombin, owns the advantage of high bioavailability and no monitoring, and was considered the drug of choice for the prevention of VTE after orthopaedic surgery. Aspirin (also known as acetylsalicylic acid), which exerts its antithrombotic effect mainly by inhibiting platelet aggregation, several studies in recent years have confirmed that aspirin is also well tolerated and effective in reducing the incidence of VTE after orthopaedic surgery [7,8]. The AAOS suggested in the 2012 Evidence-Based Guidelines for Antithrombotic and Thrombolytic Medicine, 9th edition and beyond, that aspirin can also be used for postoperative antithrombotic therapy after major orthopaedic surgery (class 1B) [6]. As the most commonly used thromboprophylactic agents, there are many clinical studies comparing the efficacy and safety of LMWH and aspirin, but their conclusions lack consistency.

Several meta-analyses have summarized and reviewed the published related articles, but the opposite results have been obtained [9,10]. These articles still have defects such as small sample sizes or inclusion of retrospective studies, so the reliability of the results is questionable. In the last 2 years, new large randomized controlled trials have been performed with the use of aspirin and LMWH [11,12]. Whether aspirin or LMWH is the best treatment option for thromboprophylaxis after orthopaedic surgery remains unclear. Therefore, this meta-analysis was conducted to determine current rates of deep venous thrombosis(DVT)/Pulmonary embolism

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(PE) events, major bleeding events, wound complications, wound infection and death from randomized trials of aspirin and LMWH use in patients after orthopaedic surgery.

Materials and methods

Literature search

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [13], a systematic literature search was performed using PubMed, Embase, and Cochrane Library to identify eligible studies. The authors used following keywords with the Boolean operators 'AND' or 'OR' for the online search: 'aspirin', 'Low-Molecular-Weight Heparin', 'venous thromboembolism', 'orthopaedic surgery'. The complete search strategy of the literature was shown in Supplementary Table 1, http://links.lww.com/BCF/A173. Medical subject heading (MeSH) and full-text word was combined to develop the search strategy. Moreover, reference lists of included articles and reviews were manually searched for additional eligible articles. The final search was performed on 25 April 2023.

Selection criteria

The following selection criteria were employed to perform the analysis according to Population-Intervention-Comparison-Outcome-Study design (PICOS) principles. Population (P): adult patients who underwent an extremity or pelvis/acetabulum fracture or osteoarthritis that was treated operatively. Intervention (I): receive aspirin for thromboprophylaxis after surgery. Comparison (C): receive LMWH for thromboprophylaxis after surgery. Outcome (O): at least one accurate outcome of DVT events, PE events, major bleeding events, wound complications, wound infection and death was reported. Study design (S): RCTs published in English. Studies enrolling patients less than 18 years old, or lacking sufficient data for extraction were excluded from this meta-analysis.

Quality assessment

The Cochrane risk bias assessment tool was used to evaluate the quality of the included RCTs. We evaluated each RCT through the following seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The quality of the assessment was divided into 'low risk', 'unclear' and 'high risk'.

Data extraction

Two reviewers independently screened the titles and abstracts of relevant studies, and excluded those that did not meet the criteria. The full texts of the selected studies were retrieved to make the terminal decisions. Disagreements between reviewers on issues of research evaluation were resolved through discussion. The extracted data included: the first author, publication year, region, number of patients, time of follow-up, age, basic characteristics of studies, medication regimen of VTE prophylaxis, and major end points. Major end points were encompassed DVT events, PE events, major bleeding events, wound complications, wound infection and death. Major bleeding events included fatal bleeding, symptomatic bleeding into a critical area or organ, or bleeding that caused a 20 g/l decrease or more in haemoglobin level or led to transfusion of two or more units of whole blood or red blood cells, bleeding that led to reoperation. Wound complications included wound drainage, hematoma or seroma of an orthopaedic injury that led to subsequent surgery.

Statistical analysis

RevMan5.3 software was used for statistical analysis. Continuous variables were expressed by mean difference or standardized mean difference (SMD) with a 95% CI whereas dichotomous variables were expressed by odds ratio (OR) with a 95% CI for statistical analysis. The overall effects were determined by the z-test and P less than 0.05 was considered statistically significant. The chi-squared test and I^2 statistic were used to assess the heterogeneity among the results in this meta-analysis. P less than 0.1 or I^2 greater than 50% indicated that the heterogeneity was significant, and the random effects model was used. Otherwise, the fixed effects model was used. In addition, funnel plots were used to estimate possible publication bias.

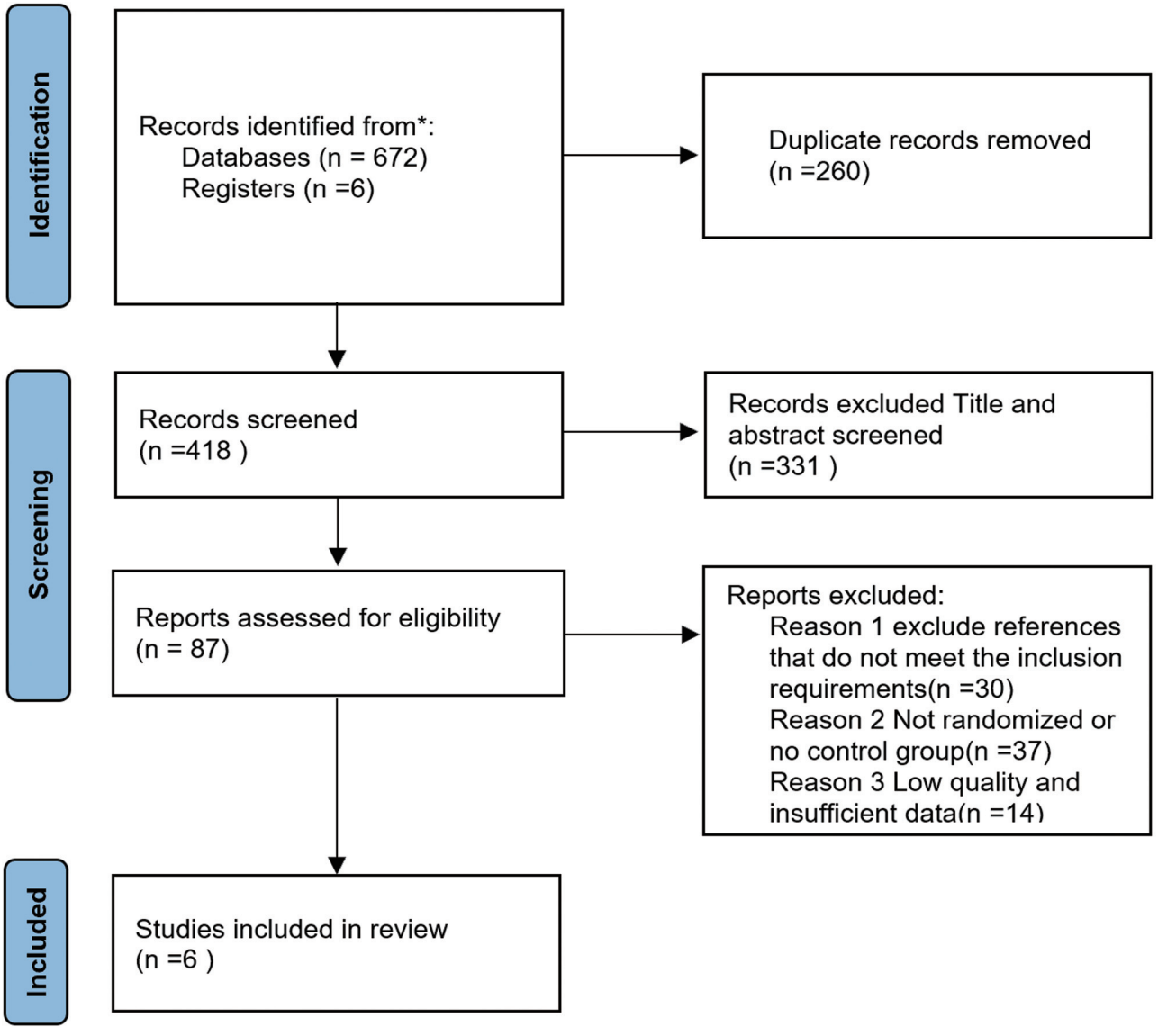
Results

Study selection and characteristics

Around 678 records were found through initial searching. Five hundred and ninety-one articles were excluded after removal of duplicates and screening of titles and abstracts according to the inclusion and exclusion criteria. After evaluating the full text, six studies were eventually included in the meta-analysis [11,12,14–17]. The study selection flow chart is shown in Fig. 1.

The basic characteristics of included studies were summarized in Table 1. A total of 23 327 patients were enrolled, including 12 470 in the aspirin group and 10 857 in the LMWH group. Three studies [12,14,15] were from North America, two studies [16,17] were from China and one was from Australia. Three studies [15–17] included patients who underwent TKA only, one study [14] included patients who underwent THA only, and one study [11] included patients who underwent either TKA or THA. Three trials [11,12,15] compared aspirin versus enoxaparin for VTE prophylaxis following orthopaedic surgery, two trials [14,16] compared aspirin versus dalteparin, and one trial [17] did not mention the specific type of LMWH. All studies reported DVT events, and three studies reported PE events. The medication regimen of VTE prophylaxis were shown in Table 2. Aspirin doses ranged from 81 mg once daily to 325 mg twice daily, with duration of treatment ranging from 2 to 5 weeks.

Fig. 1



Preferred reporting items for systematic reviews and meta-analyses flow chart for article selection.

Table 1 Characteristics of studies

				Patients		Age			
Studies (first author, year)	Year	Country	Surgical procedure	Aspirin	LMWH	Aspirin	LMWH	Comparison	Follow-up
Anderson, 2013 [14]	2013	Canada	THA	385	400	57.6 ± 11.9	57.9 ± 12.2	Aspirin vs. dalteparin	90 days
Sidhu, 2022 [11]	2022	Australia	THA, TKA	5675	4036	67	68	aspirin vs. enoxaparin	90 days
O'Toole, 2023 [12]	2023	America, Canada	major orthopaedic surgery	6101	6110	44.5 ± 18.0	44.7 ± 17.6	aspirin vs. enoxaparin	90 days
Westrich, 2006 [15]	2006	America	TKA	139	139	69.0 ± 12.1	68.9 ± 9.6	aspirin vs. enoxaparin	4–6 weeks
Zhou, 2023 [16]	2023	China	TKA	60	60	66.4 ± 7.6	64.1 ± 6.7	Aspirin vs. dalteparin	90 days
Zou, 2014 [17]	2014	China	TKA	110	112	62.7	65.7	aspirin vs. LMWH	4 weeks

LMWH, low-molecular-weight heparin; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Table 2 Medication regimen of venous thromboembolism events prophylaxis

Studies	Aspirin	LMWH
Anderson, 2013 [14]	81 mg of aspirin orally once daily for 28 more days	5000 U of dalteparin once daily for 28 more days
Sidhu, 2022 [11]	100 mg/day of aspirin orally for 35 days after hip arthroplasty and for 14 days after knee arthroplasty	40 mg/day of enoxaparin subcutaneously for the same time periods, with the dose reduced to 20 mg for patients weighing less than 50 kg and for patients with an estimated glomerular filtration rate less than 30 ml/min/1.73 m^2
O'Toole, 2023 [12]	81 mg of aspirin twice daily	30 mg of enoxaparin twice daily
Westrich, 2006 [15]	325 mg of enteric-coated aspirin twice daily for 4 weeks postoperatively	30 mg of enoxaparin twice daily until their hospital discharge; upon discharge, 40 mg once daily for 3 weeks
Zhou, 2023 [16]	100 mg of aspirin orally once daily for 30 days	2500 U of dalteparin once daily for 30 days
Zou, 2014 [17]	100 mg of aspirin orally once daily for 14 days	4000 U of subcutaneous LMWH once daily for 14 days

LMWH, low-molecular-weight heparin.

LMWH doses ranged from 32 mg once daily to 30 mg twice daily, with duration of treatment ranging from 2 to 5 weeks.

Meta-analysis results

Venous thromboembolism events

Six of included studies [11,12,14–17] reported VTE events. The rates of VTE events were 459 out of 12 159 (3.8%) in the aspirin group and 288 out of 10 566 (2.7%) in the LMWH group. The pooled result showed that there was a significant difference between the two groups (OR 1.44, 95% CI 1.24–1.68, $P < 0.00001$, Fig. 2a). the risk of VTE events after orthopaedic surgery in patients receiving aspirin was statistically higher than the risk in patients receiving LMWH. However, given the high heterogeneity of the results, we analysed the two most common thrombotic events, DVT and PE, according to VTE site. There were six [11,12,14–17] and three [11,12,17] of included studies reported DVT and PE events, respectively. The result showed that there was a significant difference between the two groups in DVT events (OR 1.59, 95% CI 1.33–1.91, $P < 0.00001$, Fig. 2b) while was not in PE events (OR 1.22, 95% CI 0.62–2.40, $P = 0.56$, Fig. 2c).

Major bleeding events

Four studies [11,12,14,16] provided data on major bleeding events. There was no significant difference between the aspirin group and the LMWH group (OR 0.95, 95% CI 0.86–1.05, $P = 0.33$, Fig. 3).

Wound complications

Wound complications were investigated in three studies [12,14,17]. The incidence of wound complications was similar between the groups, and the difference was not statistically significant (OR 0.58, 95% CI 0.28–1.17, $P = 0.13$, Fig. 4).

Wound infection

Two trials [12,14] reported wound infection during the follow-up time. Data from included trials revealed no significant difference between the two groups (OR 1.12, 95% CI 0.86–1.47, $P = 0.39$, Fig. 5).

Death

Three studies [11,12,14] reported the death of patients, and no significant difference was observed between the aspirin group and the LMWH group (OR 1.04, 95% CI 0.70–1.55, $P = 0.83$, Fig. 6).

Quality assessments

The quality assessment results of RCTs was listed in Fig. 7. Most RCTs had a low risk of bias in seven aspects such as random sequence generation, allocation concealment. Overall, the studies were of intermediate to low risk and of good quality.

Sensitivity analysis

Sensitivity analysis was performed for outcomes with I^2 greater than 50%, and after each study was excluded one by one, both I^2 and results did not change significantly, suggesting that the meta-analysis was stable and the results were reliable.

Bias analysis

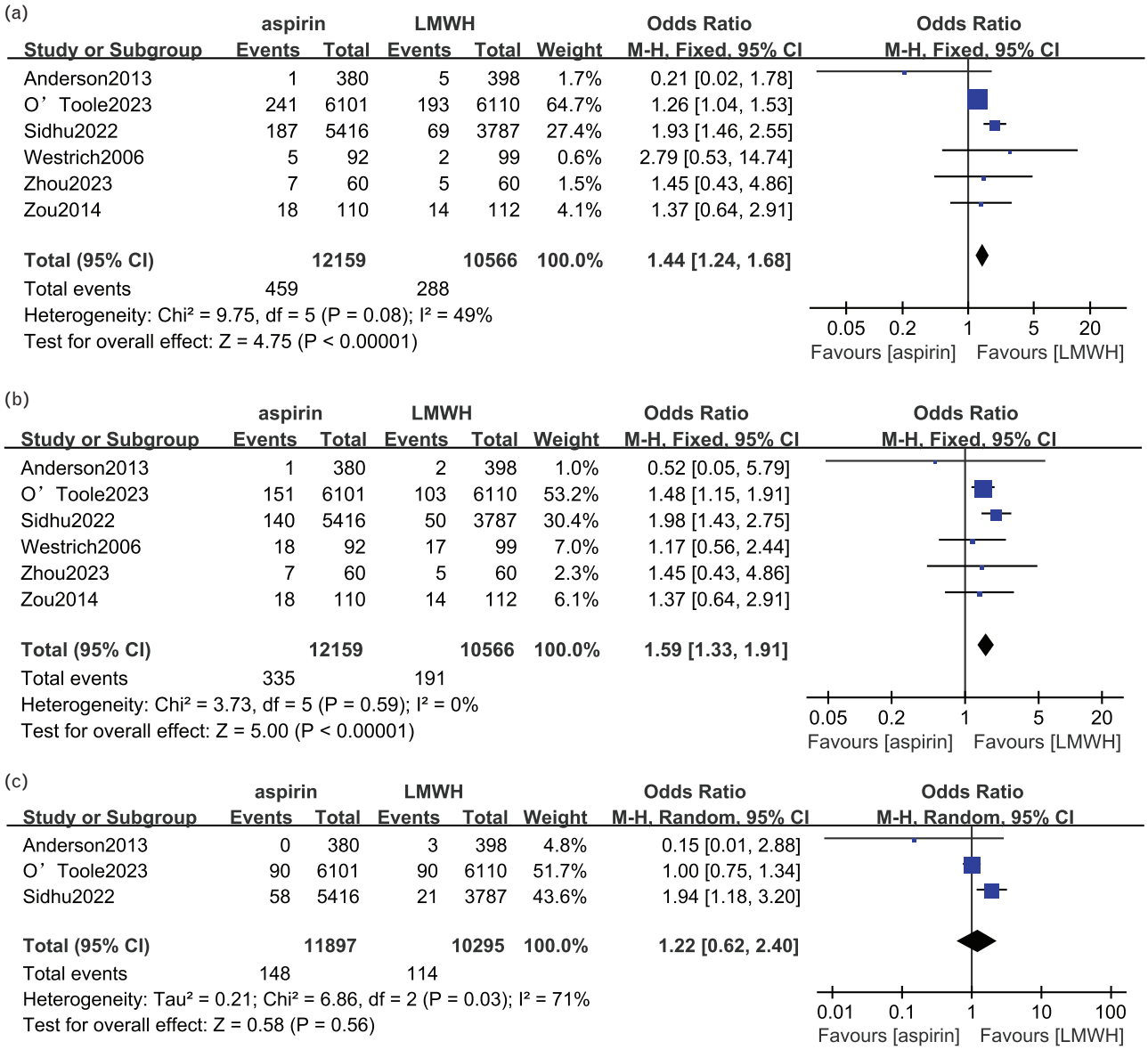
Funnel plots of VTE and DVT among the aspirin group and the LMWH group were performed (Supplementary Figure 1, http://links.lww.com/BCF/A172). All studies were included in the funnel plots. Visual inspection of plots for studies of them were symmetrical, which were consistent with Egger regression symmetry tests (VTE: $t = -0.59$, $P = 0.586$; DVT: $t = -1.21$, $P = 0.292$), demonstrating no statistically significant evidence of publication bias.

Discussion

Due to the damage to the venous blood vessel wall caused by surgical trauma and restrictions of diet and activity, patients who suffered orthopaedic surgery are prone to a hypercoagulable state of blood and eventually DVT events occurred [18,19]. The standardized use of anticoagulants such as aspirin and LMWH can reduce the risk of DVT after surgery, alleviate patients' pain, and have positive significance in promoting patients' recovery process and shortening hospitalization time [20–22].

The comparative efficacy of aspirin and LMWH, the two most popular drugs for VTE prevention in recent years, is

Fig. 2

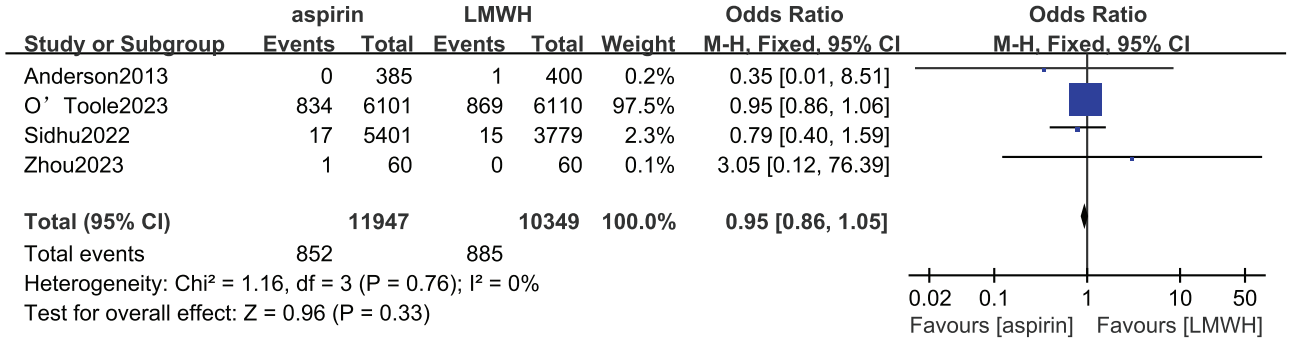


(a) Forest plot of the result comparing aspirin versus low-molecular-weight heparin for venous thromboembolism events. (b) Forest plot of the result comparing aspirin versus low-molecular-weight heparin (LMWH) for DVT events. (c) Forest plot of the result comparing aspirin versus LMWH for PE events. CI, confidence intervals; DVT, deep venous thrombosis; Fixed, a Fixed effects model; M–H, Mantel–Haenszel test; PE, Pulmonary embolism; Random, a random effects model.

still controversial. In this study, a meta-analysis of the efficacy of aspirin and LMWH for thromboprophylaxis after orthopaedic surgery was conducted, and the results showed that LMWH was superior to aspirin in preventing VTE, whereas there was no significant difference between them in safety. This result is consistent with the study by Snyder *et al.* [23]. In addition, we performed a subgroup analysis of VTE events, which showed that compared with aspirin, LMWH was more likely to reduce the incidence of DVT events in orthopaedic surgery patients, whereas there was no advantage in reducing the incidence of PE events.

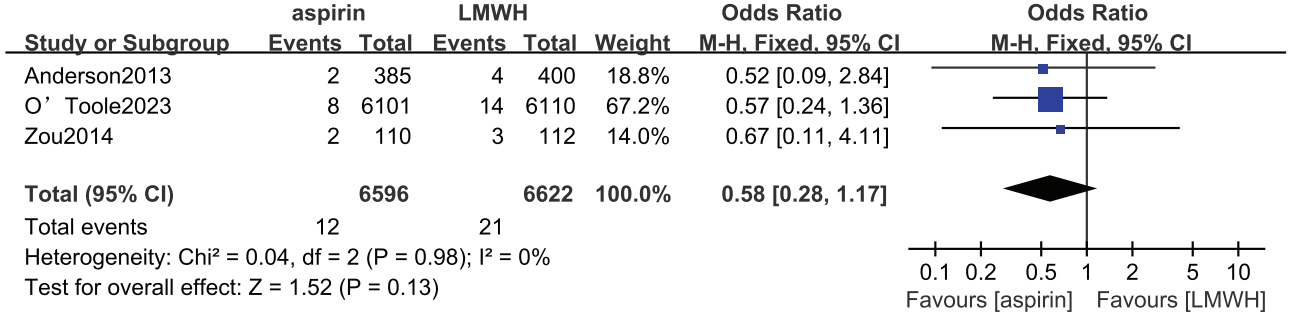
In this meta-analysis, two important recently published randomized controlled trials [11,12] that included more than 90% of the patients in our systematic evaluation and meta-analysis was included, representing 41.2 and 51.9%, respectively. To date, these two large trials have not been considered in any prior meta and therefore may alter the interpretation of the available data. Notably, the results

Fig. 3



Forest plot of the result comparing aspirin versus low-molecular-weight heparin for major bleeding events. CI, confidence intervals; Fixed, a Fixed effects model; M–H, Mantel–Haenszel test.

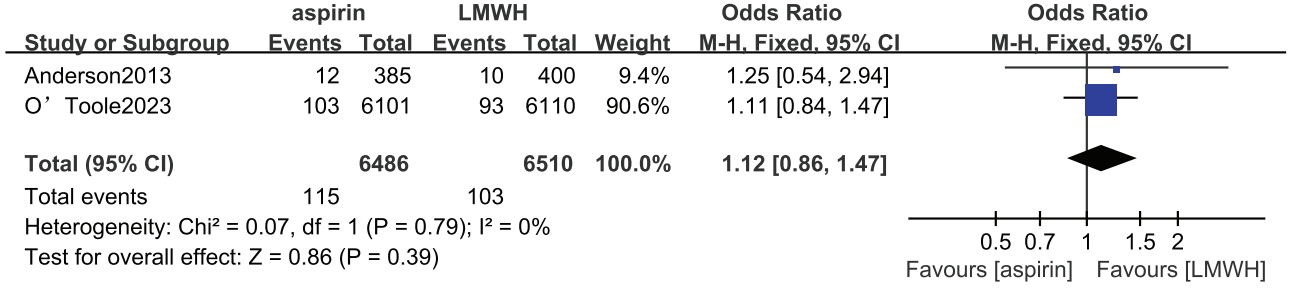
Fig. 4



Forest plot of the result comparing aspirin versus low-molecular-weight heparin for wound complications. CI, confidence intervals; Fixed, a Fixed effects model; M–H, Mantel–Haenszel test.

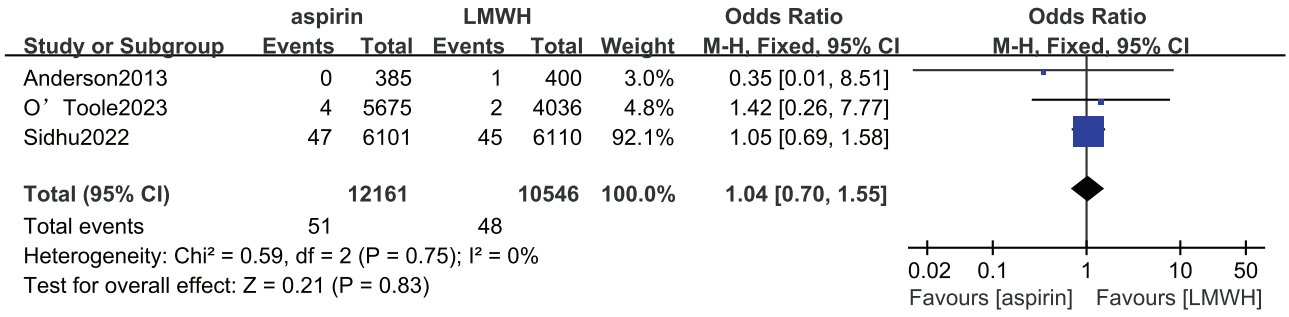
of them were diametrically opposed. Sidhu *et al.* [11] observed no difference between aspirin and low-molecular heparin in the prevention of VTE, whereas O'Toole *et al.* [12] concluded that aspirin was associated with a lower incidence of DVT and PE and a lower 90-day mortality rate. However, regardless of the exclusion of either of these two RCTs, the analysis also demonstrated that there was a statistically significantly difference between LMWH and aspirin, and LMWH owned superiority over aspirin for thromboprophylaxis.

Fig. 5



Forest plot of the result comparing aspirin versus low-molecular-weight heparin for wound infection. CI, confidence intervals; M–H, Mantel–Haenszel test; Random, a random effects model.

Fig. 6

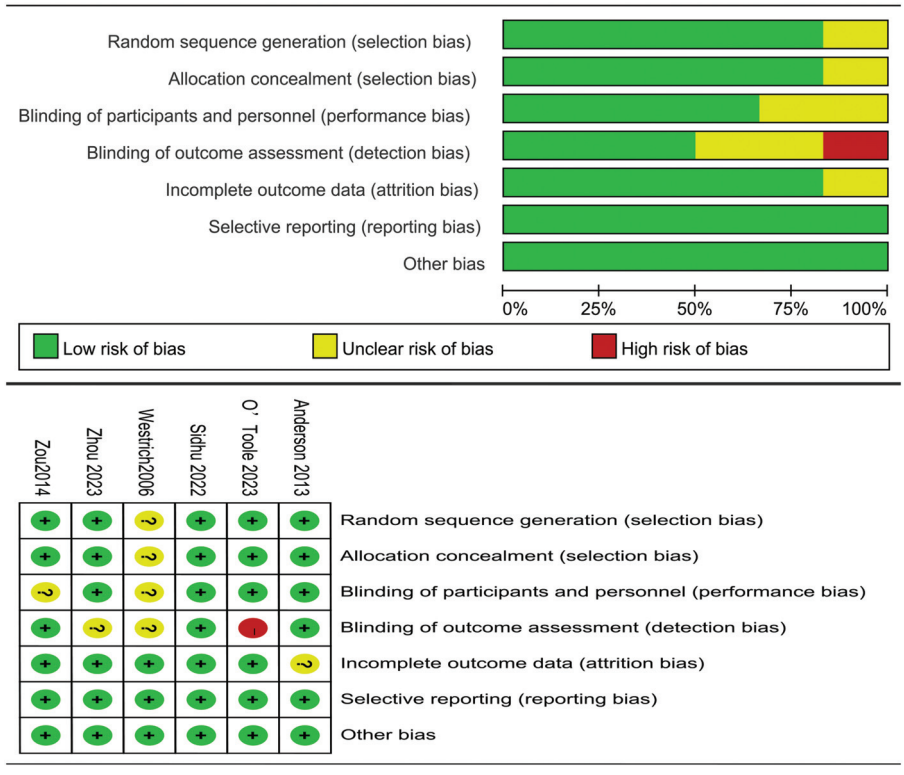


Forest plot of the result comparing aspirin versus low-molecular-weight heparin for death. CI, confidence intervals; Fixed, a Fixed effects model; M–H, Mantel–Haenszel test.

In terms of safety, there were no significant differences in mortality, bleeding events, wound complication and wound infection outcomes between the two drugs, which is similar to the results reported in previous studies [11,12,24–26]. In addition, it has also been shown that aspirin does not increase the risk of transfusion in patients compared with other anticoagulants such as LMWH and rivaroxaban [27].

In the included RCTs, although half of the studies used an aspirin dose of 81 mg twice daily, there were studies that used a nonstandard dose of 100 mg daily and 325 mg twice daily. However, we do not think different doses of aspirin biased our results. In a 3-year retrospective multicentre cohort study by Watts *et al.* [28], they compared the odds of bleeding and VTE between different aspirin dosages (81, 162, 325, or 650 mg) after

Fig. 7



Quality assessment of the included studies.

lower extremity arthroplasty or revision, and their study showed no significant difference in the rates of bleeding or venous thromboembolism for all aspirin doses. Tang *et al.* [29] also suggested that the clinical outcomes and safety of the two protocols of aspirin 325 mg twice daily and 81 mg twice daily after knee arthroplasty were similar.

This meta-analysis had several strengths. First of all, this study included several RCTs with larger sample sizes that were never covered by previous studies, thus providing the most comprehensive update on the efficacy and safety of aspirin and LMWH in the prevention of VTE after orthopaedic surgery. Secondly, our article includes only RCT studies, so selection bias was reduced, which made our results more generalizable. Moreover, low or no heterogeneity in the most of the pooled results improved the reliability of our articles.

Of course there were limitations to this article. Due to the limitation of the number of RCTs included, we were unable to perform subgroup analysis on the type of orthopaedic surgery (THR, TKR, etc.), ethnic differences, and type of VTE (symptomatic vs. asymptomatic). In addition, differences in dose and duration of aspirin and LMWH among RCT studies also put the results at risk of bias.

Conclusion

This meta-analysis showed that LMWH was significantly superior to aspirin in thromboprophylaxis after orthopaedic surgery, despite the similar safety profiles. LMWH was still the first-line drug for thrombosis prevention in patients who underwent major orthopaedic surgeries.

Acknowledgements

Availability of data and materials: all data generated or analysed during this study are included in this published article and its supplementary information files.

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Authors' contributions: L.Z. and Q.W. collected data, T. W. analysed and interpreted data. H.W. drawn tables and pictures, and was a major contributor in writing the manuscript. S.L. was responsible for revising the article. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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