Systematic Review and Meta-Analysis

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Efficacy and safety of aspirin and rivaroxaban for venous thromboembolism prophylaxis after total hip or knee arthroplasty

A protocol for meta-analysis

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Abstract

Background: The purpose of this meta-analysis is to compare the efficacy and safety of aspirin and rivaroxaban in the prevention of venous thromboembolism (VTE) following either total knee arthroplasty or total hip arthroplasty.

Methods: A comprehensive literature search of several electronic databases (PubMed, Embase, and Web of Science) was conducted to identify relevant studies. Outcomes of interest included VTE rate, deep vein thrombosis (DVT) rate, pulmonary embolism rate, major bleeding events, mortality rate, blood transfusion, and wound complication. Risk ratio (RR) with 95% confidence intervals (95%CIs) were calculated using a fixed-effects model or random-effects model.

Results: A total of 8 studies with 97,677 patients met the inclusion criteria and were included in this meta-analysis. Compared with rivaroxaban, aspirin had a significantly higher incidence of DVT (RR = 1.48, 95%CI: 1.27, 1.72; $P < .001$), and decreased risk of blood transfusion (RR = 0.94, 95%CI: 0.93, 0.94; $P < .001$). However, there were no significant differences between the 2 drugs in terms of total VTE rate (RR = 1.39%, 95%CI: 0.94, 2.05; $P = .101$), pulmonary embolism rate (RR = 1.64, 95%CI: 0.92, 2.92; $P = .094$), mortality rate (RR = 1.13, 95%CI: 0.15, 8.27; $P = .907$), major bleeding (RR = 1.00, 95%CI: 0.44, 2.27; $P = .995$), and wound complication rate (RR = 0.37, 95%CI: 0.07, 1.87; $P = .229$).

Conclusion: Our results suggested that aspirin and rivaroxaban offered similar effect in the prevention of VTE after total knee arthroplasty or total hip arthroplasty. However, rivaroxaban seemed to have better effect than aspirin in reducing the risk of DVT, and aspirin was safer than rivaroxaban in decreasing the blood transfusion rate.

Abbreviations: CIs = confidence intervals, DVT = deep vein thrombosis, LMWH = low molecular weight heparin, NOS = Newcastle-Ottawa scale, PE = pulmonary embolism, RR = risk ratio, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

Keywords: aspirin, meta-analysis, rivaroxaban, total hip arthroplasty, total knee arthroplasty

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GL and CY contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), and pulmonary embolism (PE), is one of the well-recognized complications after total hip (THA) or total knee arthroplasty (TKA).[1,2] The reported incidences of DVT and PE following THA range from less than 1% to 62.5%,[3–5] which could be explained by the differences in surgical technique, length of hospital stay, mechanical preventive device use, ethnicity, and preventive measures.[5] Among these factors, thromboprophylaxis is one of the major factors that influence the occurrence of VTE.[6]When thromboprophylaxis is not used, the incidence of DVT and fatal PE may reach 60% and 1.5%, respectively.[7,8]

Aspirin, as an effective VTE prophylaxis after THA and TKA, has been widely used; however, its efficacy and safety in comparison with other anticoagulants remain controversial.[9] In the recently published studies, aspirin showed effective prevention for postoperative VTE, with lower risk of complications, such as wound infection, bleeding, rehospitalization, and even mortality.[10,11] Haykal, et al[12] conducted a meta-analysis of 13 RCTs and reported that aspirin was associated with a significant reduction of VTE (risk ratio [RR] = 0.65, 95%CI: 0.47, 0.89; $P = .008$) as compared with placebo.[12] Moreover, there were no significant differences between them in terms of mortality (RR = 0.97, 95%CI: 0.86, 1.10) and major bleeding events (RR = 0.57, 95%CI: 0.15, 2.17).[12] This indicated that aspirin had better effects in reducing VTE than placebo. Rivaroxaban, widely used as another available anticoagulant, also showed good effects in the prevention of VTE postoperatively. Gomez-Outes, et al[13] reported that rivaroxaban significantly reduced the incidences of symptomatic VTE (RR = 0.48, 95CI; 0.31, 0.75), but also increased the risk of clinically relevant bleeding (RR = 1.25, 95%CI: 1.05, 1.49).

Although there have been several trials that compared the efficacy and safety of aspirin and rivaroxaban in the prevention of VTE after THA or TKA, a meta-analysis with such a direct comparison between them has yet to be conducted. Therefore, we carried out this meta-analysis to evaluate the efficacy and safety of aspirin with rivaroxaban in preventing VTE for patients who underwent TKA or THA.

2. Materials and methods

2.1. Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analysis criteria.[14] PubMed, Embase, and Web of Science database were searched from their inception to March 15, 2020 to identify relevant studies. Search terms were used as followings: ("arthroplasty, replacement, hip" [MeSH terms] or ("arthroplasty" [all fields] and "replacement" [all fields] and "hip" [all fields]) or "hip replacement arthroplasty" [all fields] or ("total" [all fields] and "hip" [all fields] and "arthroplasty" [all fields]) or "total hip arthroplasty" [all fields]) or (total [all fields] and knee [all fields] and ("arthroplasty" [MeSH terms] or "arthroplasty" [all fields])) and ("aspirin" [MeSH terms] or "aspirin" [all fields]) and ("rivaroxaban" [MeSH terms] or "rivaroxaban" [all fields]). We did not impose any restriction on the language. In addition, we also manually searched the reference lists of included studies and relevant reviews to identify potentially eligible studies. The ethical approval and patient consent were not performed since the current study is based on previously published studies.

2.2. Study selection

All clinical trials that compared the efficacy and safety of aspirin and rivaroxaban in preventing VTE after TKA or THA were considered eligible for analysis. The inclusive selection criteria were applied:

(1) study design: RCT, cohort study, case-control, or comparative trial;
(2) population: adult patients who underwent TKA or THA;
(3) intervention: aspirin or rivaroxaban;
(4) outcome measures: VTE, PE, DVT, major bleeding, mortality, and wound complication.

2.3. Data extraction and quality assessment

Two independent investigators performed the data extraction. A standardized Excel file was used to extract the following data:

(1) Publication time, first authors' name, country, and study design;
(2) Characteristics of patients (sample size, mean age, gender, race, and weight);
(3) Detailed information on the treatment (dosage, administration schedule, and treatment duration);
(4) Duration of follow-up;
(5) Outcomes: VTE, DVT, PE, major bleeding mortality rate, and wound complication.

We used the modified Newcastle-Ottawa scale(NOS)[15] to assess the methodological quality of a non-RCT. This method consists of 3 items, including patient selection, comparability of the intervention/ control group, and outcome assessment.[15] The total score is 9 points, and higher score indicates better quality. Any study with a score of more than 5 points were categorized as high quality.[15]

We used the method recommended by the Cochrane Collaboration to evaluate the risk of bias in included RCTs.[16] This method consists of 7 items, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[16] Each RCT was regarded as being at low, unclear, or high risk of bias based on the abovementioned criteria.

2.4. Statistical analysis

This meta-analysis was performed using STATA software version 12.0 (Stata Corporation, College Station, TX). Dichotomous outcomes were calculated as RRs with 95% confidence intervals (CIs). Heterogeneity among the included studies was evaluated by Cochrane Q Chi-squared test and I^2 statistic,[17] in which a P value $< .1$ or $I^2 > 50\%$ represent significant heterogeneity. When significant heterogeneity was tested, a random-effects model (DerSimonian–Laird method)[18] was applied to pool the estimate; otherwise a fixed-effects model (Mantel–Haenszel method)[19] was used. We also conducted sensitivity analysis to explore the potential sources of heterogeneity when heterogeneity was substantial or obvious. We also conducted subgroup analysis based on the dosage of aspirin. The publication bias was assessed using Begg[20] and Egger test.[21] A P value less than .05 was judged as statistically significant, except where otherwise specified.

3. Results

3.1. Identification of eligible studies

Our initial search yielded a total of 1372 records, of which 683 were excluded because of duplicate records. Then 677 records were excluded after title/abstract review, leaving12 potential studies for full-text information review. However, 4 of them were excluded for the following reasons: 2 compared aspirin with other anticoagulants,[22,23] and 2 compared rivaroxaban with other anticoagulants.[24,25]Finally, 8 studies[26–33] met the inclusion criteria, and were included in this meta-analysis (Fig. 1).

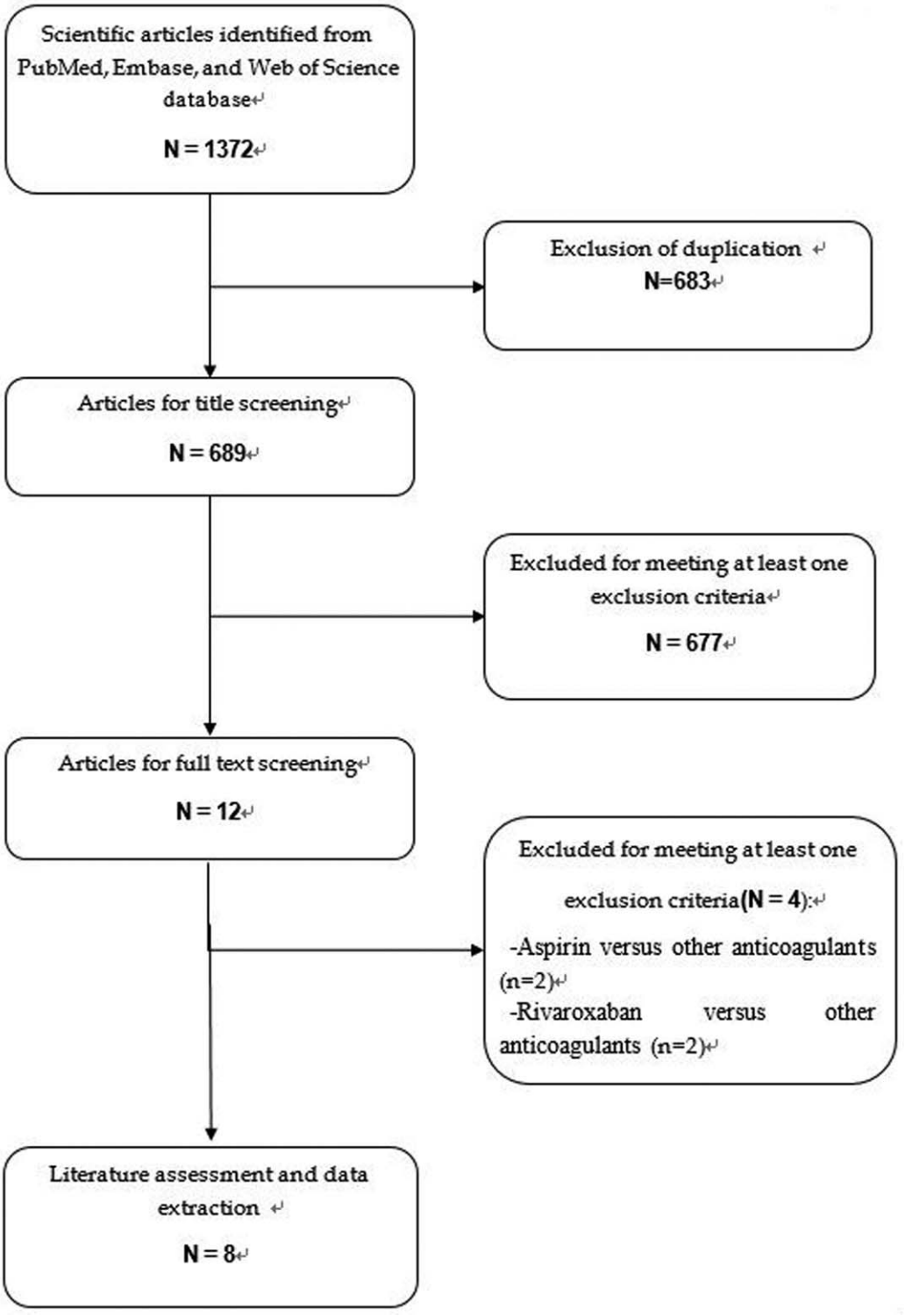

Figure 1. Eligibility of studies for inclusion in meta-analysis.

3.2. Characteristics of eligible studies and quality assessment

The main patient characteristics of the 8 included studies were presented in Table 1. These studies were published between 2014 and 2019. Of these studies, 4 were cohort studies,[26–28,30] 3 were RCTs,[29,32,33] and 1 was a case-control study.[31] These studies were carried out in China, Brazil, Korea, Thailand, and Canada. The dosage of aspirin varied greatly among the included studies, which ranged from 100 mg daily to 300 mg per day. Rivaroxaban in each study was administrated with 10 mg per day. Among the included studies, 3 studies evaluated VTE in both THA and TKA,[26,28,32] 4 studies evaluated VTE in TKA alone,[27–29,33] and 1 study evaluated VTE in THA alone.[30] The duration of follow-up ranged from 4 weeks to 3 months.

Five of the included studies were cohort or case-control studies, thus the methodological qualities were assessed using modified NOS scale. Among the 5 studies, 3 were given a NOS score of 7 points and 2 were 6 points, which indicated that these studies were of high quality.

Three of the included studies were RCT, and the risk bias assessment showed that only 1 study[32] was classified as being at low risk of bias, and the remaining 2 being at high risk of bias. The main reason for the 2 trials[29,33] with high risk of bias was that the blinding of outcome assessments was unclear or seldom reported. The adequate randomized sequence, and appropriate allocation concealment were reported in all the included trials.

3.3. VTE

Five studies reported the data of VTE.[26,28,30,32,33] The incidence of VTE in aspirin and rivaroxaban groups was 1.6% (513/32075) and 0.9% (665/73610), respectively. Pooled estimate showed that, aspirin was associated with a comparable VTE rate as compared with rivaroxaban (RR = 1.39%, 95%CI: 0.94, 2.05; $P = .101$) (Fig. 2). There was significant heterogeneity among the included studies ($I^2 = 72.4\%$, $P = .001$). Thus, sensitivity analysis was conducted. When we excluded the trial with small sample size,[33] the overall estimate changed a little (RR = 1.48, 95%CI: 0.97, 2.24; $P = .067$), but the heterogeneity was still present ($I^2 = 73.9\%$, $P = .002$). When we excluded the outlier,[30] the pooled result did not alter substantially (RR = 1.22, 95%CI: 0.79, 1.88; $P = .368$), but the heterogeneity was still identified ($I^2 = 74.5\%$, $P = .001$).

Subgroup analysis based on the dosage of aspirin showed that, aspirin had a similar incidence of VTE with rivaroxaban no matter what dosage it was administered (100 mg/d: RR = 0.92, 95%CI: 0.52, 1.61; $P = .763$; 200 mg/d: RR = 1.64, 95%CI: 0.41, 6.56; $P = .485$).

3.4. DVT

Six studies reported the data of DVT.[26–30,32] The incidence of DVT in aspirin and rivaroxaban groups was 0.91% (293/32139) and 0.57% (420/73670), respectively. The summarized result suggested that, aspirin had a significantly higher DVT rate as compared with rivaroxaban (RR = 1.48, 95%CI: 1.27, 1.72; $P < .001$) (Fig. 3). There was not substantial heterogeneity among the included studies ($I^2 = 47.1\%$, $P = .066$).

Subgroup analysis based on the dosage of aspirin demonstrated that, aspirin administered with a dosage of 100 mg daily had a significantly higher risk of developing DVT than rivaroxaban (RR = 3.01, 95%CI: 1.30, 6.98; $P = .010$); whereas the 200 mg and 300 mg of aspirin once daily was associated with a similar risk of DVT with rivaroxaban (200 mg/d: RR = 1.64, 95%CI: 0.41, 6.56, $P = .485$; 300 mg/d: RR = 0.64, 95%CI: 0.06, 6.39, $P = .706$).

3.5. PE

Three studies reported the data of PE.[26,28,32] The incidence of PE in aspirin and rivaroxaban groups was 0.76% (227/29944) and 0.33% (236/71479), respectively. Pooled result showed that, there was no significant difference in incidence of PE between the 2 groups (RR = 1.64, 95%CI: 0.92, 2.92; $P = .094$) (Fig. 4).

3.6. Mortality

Mortality was assessed in 3 studies.[27,32,33] Among these studies, 1 death was reported in each group, respectively, corresponding to a mortality rate of 0.056%. Pooled estimate showed that, no

Table 1

Baseline characteristics of patients in the trials included in the meta-analysis.

Study	Country	Study design	Treatment regimen	No. of patients	Male/female	Age (mean ± SD, yr)	Type of surgery	NOS score
Xu W[26]	China	Cohort	Aspirin 100 mg, 2 times/d for 6 weeks	61	15/46	68.2 ± 9.5	TKA or THA	7
			Rivaroxaban 10 mg, 1 times/d, for 12 days	60	17/43	67.5 ± 12.4		
Colleoni JL[27]	Brazil	Cohort	Aspirin 150 mg, 2 times/d	14	1/13	71.21 ± 6.35	TKA	6
			Rivaroxaban 10 mg/d	18	4/14	67.11 ± 7.65		
Yhim HY[28]	Korea	Cohort	NR	24612	NR	NR	TKA or THA	6
			Rivaroxaban 10 mg/d	64859	NR	NR		
Zou Y[29]	China	RCT	Aspirin 100 mg/d	110	28/82	62.7(47-79)	TKA	NA
			Rivaroxaban 10mg/d	102	32/70	63.5(50–82)		
Kim HA[30]	Korea	Cohort	Aspirin 100 mg/d	2071	NR	NR	THA	7
			Rivaroxaban 10mg/d	2071	NR	NR		
Yuenyongviwat V[31]	Thailand	Case-control	Aspirin 300 mg/d	79	10/69	70.08 ± 5.22	TKA	7
			Rivaroxaban 10 mg/d	76	9/67	71.41 ± 6.17		
Anderson DR[32]	Canada	RCT	Aspirin 100 mg/d	1707	804/903	62.9 ± 10.1	TKA or TKA	NA
			Rivaroxaban 10 mg/d	1717	833/884	62.7 ± 10.1		
Jiang Y[33]	China	RCT	Aspirin 100 mg/d	60	5/55	65.1 ± 7.5	TKA	NA
			Rivaroxaban 10mg/d	60	4/56	63.8 ± 6.7		

NA = not available, NOS = Newcastle-Ottawa scale, NR = not reported, RCT = randomized controlled trial, SD = standard deviation, THA = total hip arthroplasty, TKA = total knee arthroplasty.

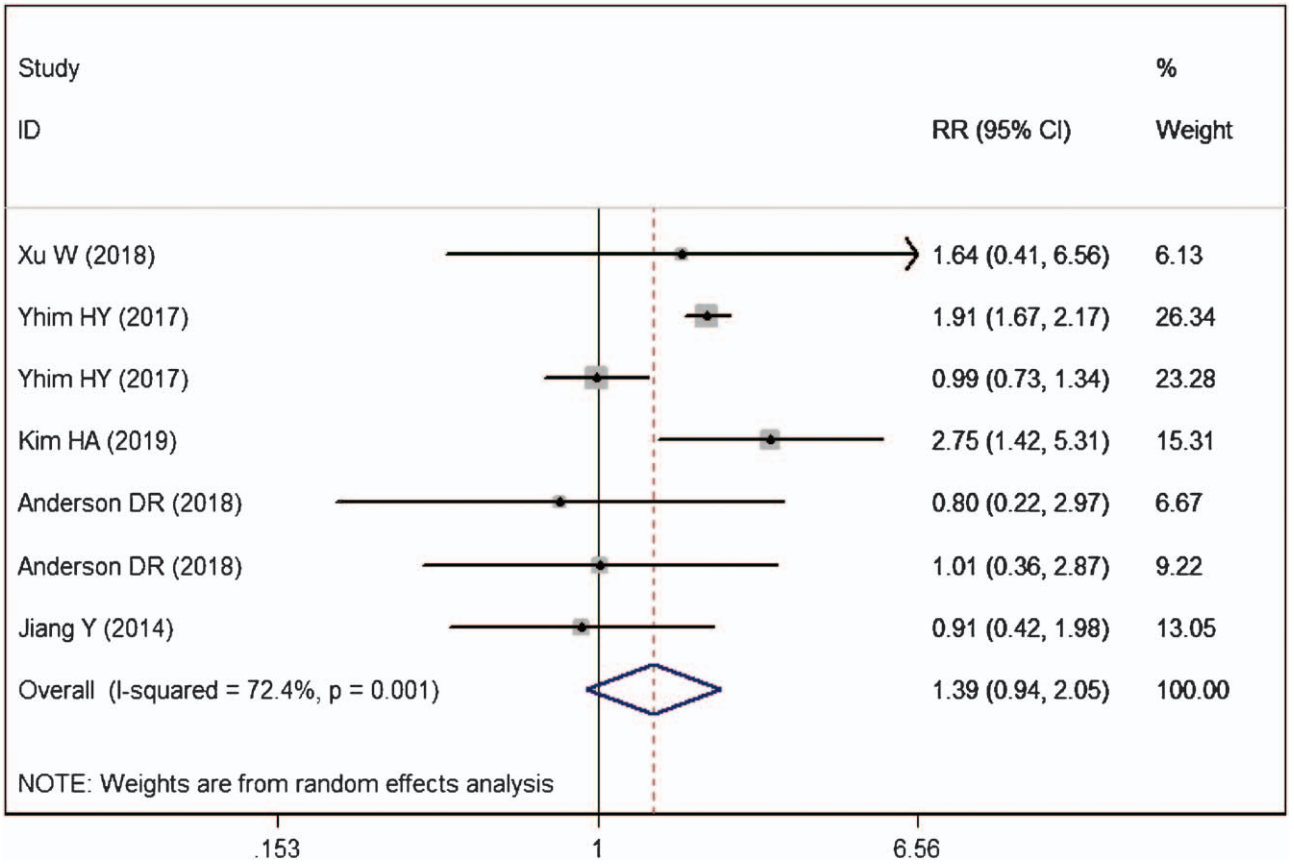

Figure 2. Forest plot showing the comparison between aspirin and rivaroxaban in venous thromboembolism.

significant difference in mortality rate was identified between the 2 groups (RR = 1.13, 95%CI: 0.15, 8.27; $P = .907$) (Fig. 5).

3.7. Major bleeding

Major bleeding was assessed in 2 studies.[26,32] Both aspirin and rivaroxaban groups reported a major bleeding incidence of 0.62%.Pooled result showed that, the incidence of major bleeding did not differ between the 2 groups (RR = 1.00, 95% CI: 0.44, 2.27; $P = .995$). The test for heterogeneity was not significant ($I^2 = 13.6\%$, $P = .314$).

3.8. Other complications

Blood transfusion was performed in 81.1% (22914/28255) of patients in aspirin group as compared with 86.6% (60457/69778) of patients in rivaroxaban group. Pooled estimate showed that aspirin was associated with a significantly lower rate of blood transfusion than rivaroxaban (RR = 0.94, 95%CI: 0.93, 0.94; $P < .001$). Wound complication rate was higher in rivaroxaban group (4.9%) than in aspirin group (1.8%). However, the difference between them was not significant (RR = 0.37, 95%CI: 0.07, 1.87; $P = .229$).

3.9. Publication bias

Since the number of included studies was less than 10, assessment of publication bias was not performed.

4. Discussion

The purpose of this meta-analysis was to compare the efficacy and safety of aspirin and rivaroxaban in preventing VTE after TKA or THA. Our results suggested that, rivaroxaban was more effective than aspirin in reducing the incidence of DVT; whereas, they were similarly effective for preventing VTE and PE. Blood transfusion rate was significantly lower in aspirin group compared with rivaroxaban group. There were no significant differences between the 2 groups in terms of major bleeding and wound complication.

There have been several published meta-analyses that compared the efficacy and safety of aspirin with placebo or other anticoagulants for the prevention of VTE after TKA or THA.[12,34,35] Two were published in 2019, and 1 in 2016. However, their results regarding the effect and safety comparison between aspirin and other anticoagulants remained inconsistent. Wilson, et al[35] conducted a systematic review of studies published between 2004 and 2014 to compare the effect of aspirin for thromboprophylaxis with other chemoprophylactic agents. They included 13 eligible studies, 5 of which were level I evidence and 8 were level III evidence. Based on these studies with moderate or severe risk of bias, the authors thought that there was insufficient evidence to suggest aspirin was more or less effective than low molecular weight heparin (LMWH), warfarin, or dabigatran for reducing the risk of VTE.[35] However, in the comparison with rivaroxaban, aspirin showed a significantly reduced incidence of asymptomatic DVT.[35] Nadi, et al[34]

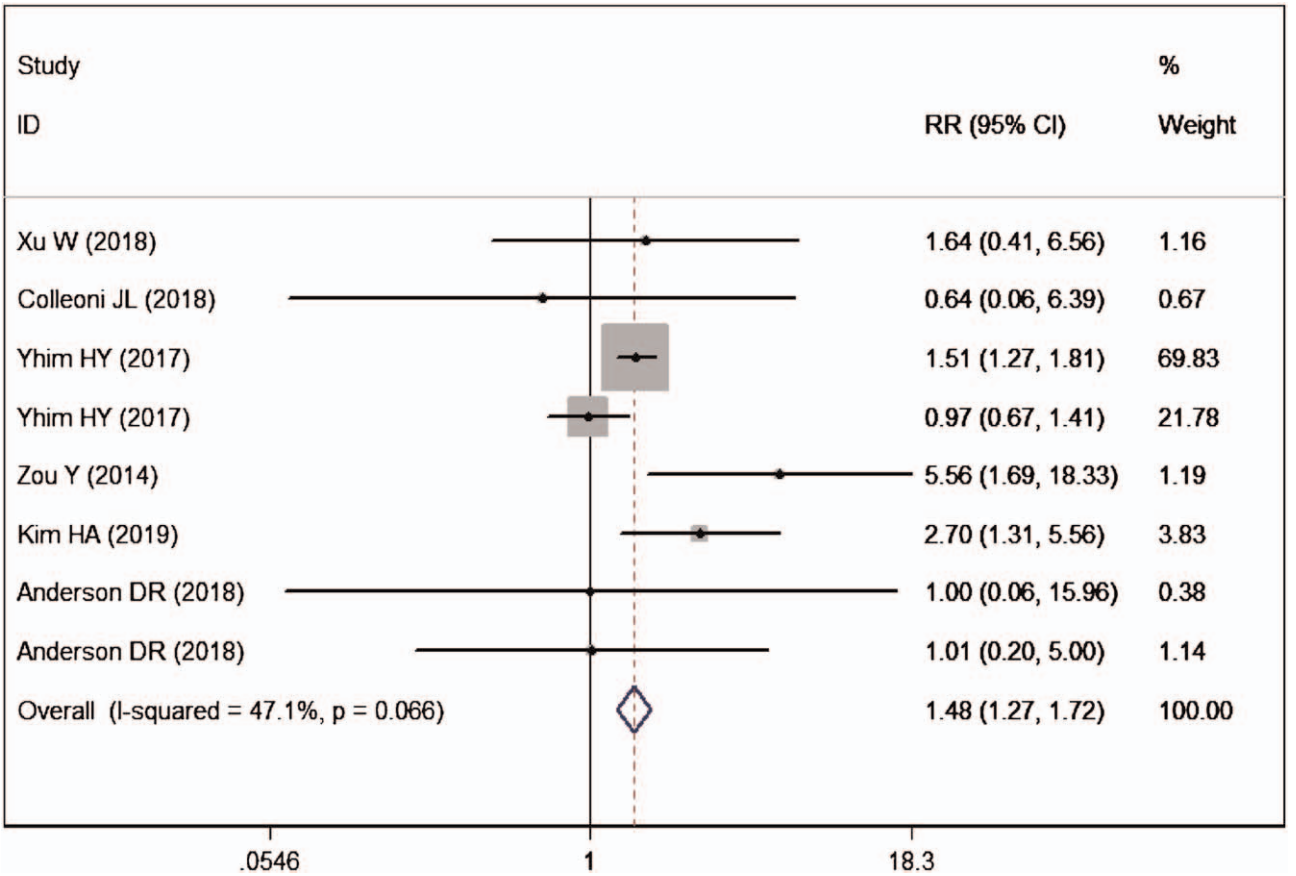

Figure 3. Forest plot showing the comparison between aspirin and rivaroxaban in deep vein thrombosis.

carried out a network meta-analysis in 2019 to compare the benefits and risks of aspirin with enoxaparin or placebo in patients undergoing THA or TKA. In that study, 9 RCTs were included. Their results suggested that there were no significant differences in total DVT rates (RR = 1.27, 95%CI: 0.84, 1.96) and symptomatic PE rates (RR = 1.02, 95%CI: 0.00, 242.90) between aspirin and enoxaparin. Regarding the postoperative complications, including wound complication (RR = 0.73, 95% CI: 0.17, 3.20) and major haemorrhage (RR = 0.97, 95%CI: 0.09, 50.99), aspirin also showed non-significant differences with enoxaparin.[34]

Similar results were reported by Haykal, et al,[12] who performed an updated meta-analysis of RCTs to compare aspirin with anticoagulants or placebo in patients who underwent knee or hip arthroplasty. This meta-analysis was published in 2019 with 13 RCTs involving 20,115 patients. The overall results suggested that there was a non-significant difference in VTE rate between aspirin and other thromboprophylactic methods (RR = 0.87, 95%CI: 0.61, 1.23; $P = .43$).[12] Whereas, aspirin was associated with a significantly decreased VTE than placebo (RR = 0.65, 95%CI: 0.47, 0.89; $P = .008$).[12] Regard to other clinical outcomes, such as mortality (RR = 0.98, 95%: 0.86, 1.11; $P = .72$), major bleeding events (RR = 0.96, 0.50, 1.84; $P = .91$), and any bleeding events (RR = 1.09, 0.82, 1.44; $P = .56$), aspirin showed non-significant differences with other anticoagulants in these outcomes.[12] The authors concluded that aspirin was associated with similar effect and safety with anticoagulants in patients undergoing knee or hip arthroplasty. Contrast to their results, Richardson, et al[36] reported a significant difference in prevention of VTE between aspirin and anticoagulants in anticoagulation-native patients who underwent TKA. In that study, the authors used a national private insurance database to assess the VTE rate between different anticoagulants. Results from 30,813 patients showed that, compared with aspirin, LMWH [odd ratio (OR) = 0.47, 95%CI: 0.29, 0.83], factor Xa inhibitors (OR = 0.50, 95%CI: 0.30, 0.89), and fondaparinux (OR = 0.32, 95%CI: 0.16, 0.64) significantly reduced the risk of VTE, but warfarin showed a trend towards a decreased risk (OR = 0.59, 95%CI: 0.36, 1.04; $P = .50$).[36] Moreover, LMWH (OR = 1.56, 95%CI: 1.07, 2.39) and fondaparinux (OR = 1.84, 95%CI: 1.23, 2.87) were associated with higher risk of transfusion than aspirin.[36] The authors stated that the lower risk of VTE with anticoagulants than aspirin might be explained by the following possible reasons. Patients enrolled in their cohort study were specifically those who underwent primary TKA. Whereas, in the previous meta-analysis, they included patients with primary and revision TKA and THA. Aspirin was more effective in THA than in TKA. Therefore, combining the procedures might bias their results.[36]

In the present study, we found that there were no significant differences between aspirin and rivaroxaban with regard to VTE rate, mortality, and major bleeding events. Our results were in concordance with the findings reported by Haykal, et al.[12] Although this study was an updated meta-analysis which

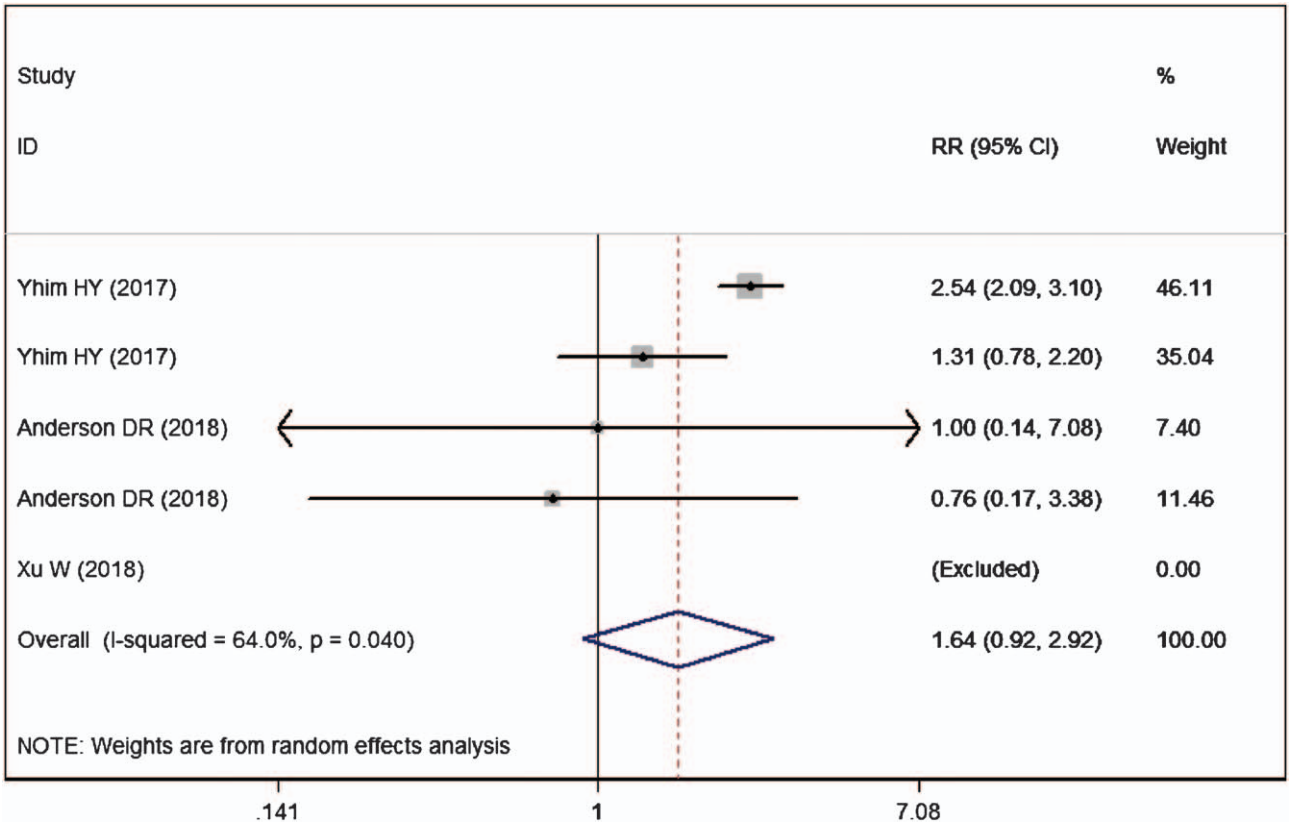

Figure 4. Forest plot showing the comparison between aspirin and rivaroxaban in pulmonary embolism.

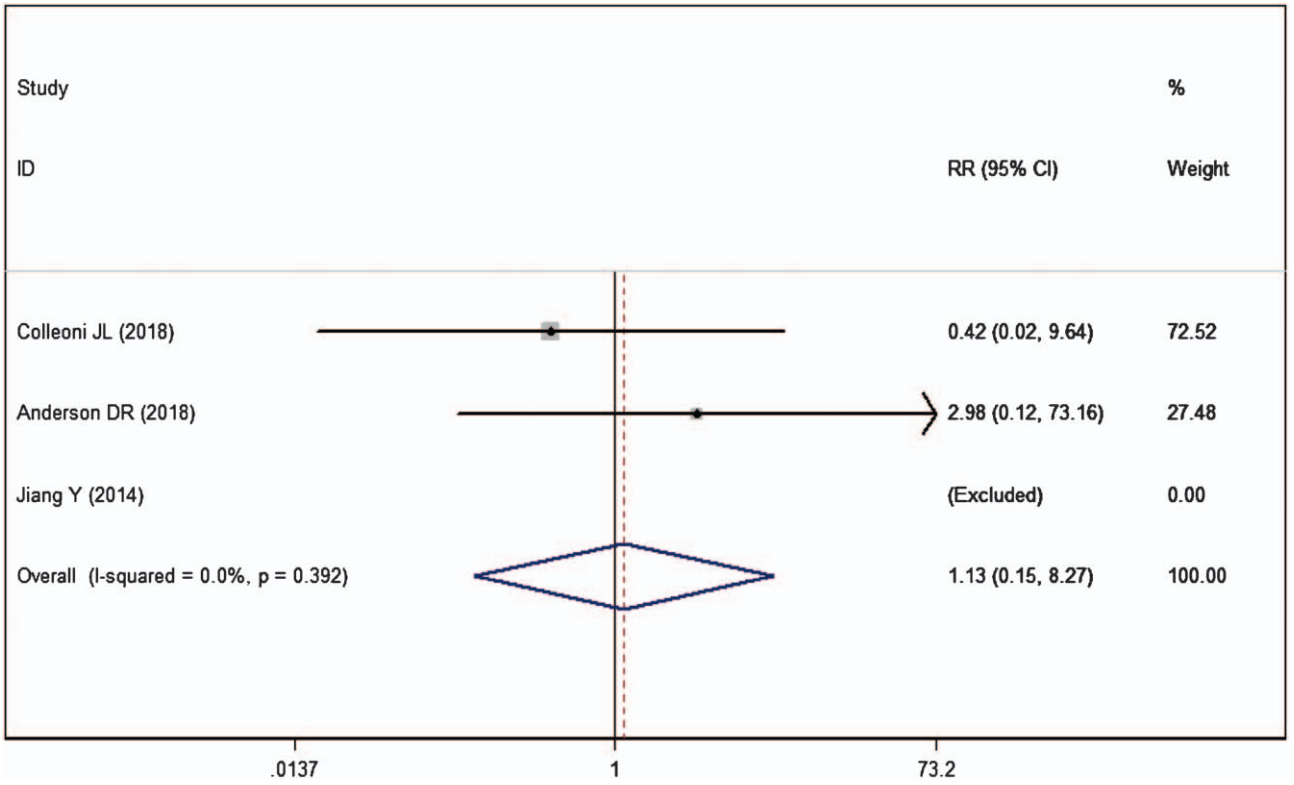

Figure 5. Forest plot showing the comparison between aspirin and rivaroxaban in mortality rate.

expanded on this earlier meta-analysis, our results provided better characterization of the evidence base for aspirin and rivaroxaban in prevention of VTE after either TKA or THA. First, in this study, there were more included studies and enlarged sample sizes than the previous analysis, which enhanced the statistical power to assess the effects and safety. In this study, we included 8 studies with 97,677 patients. Whereas, in the previous study,[12] there were only 3 studies with 3756 patients focusing on the comparison between aspirin and rivaroxaban. Second, based on the previous meta-analysis, we furthermore included 5 recent studies.[26–28,30,31] With the added statistical power of having 93,921 patients, our study showed that, aspirin was associated with comparable outcomes than rivaroxaban, including VTE, mortality, major bleeding events, which in agreement with the previous meta-analysis.[12] Moreover, the sensitivity analysis by exclusion of any single study did not substantially change the overall estimate, which confirmed the reliability and credibility of our findings. Third, we also compared the effects of 2 drugs on DVT, PE, blood transfusion, and wound complications, which had not been discussed in the prior meta-analysis.[12]

In the present analysis, aspirin was as effective as rivaroxaban in the prevention of VTE after THA or TKA. However, in the terms of DVT, aspirin showed an increased risk than rivaroxaban. This result was in consistent with most of the published studies.[26,30,32] Xu, et al[26] performed a cohort study to compare the efficacy and safety of 3 anticoagulants (aspirin, LMWH, and rivaroxaban) in preventing VTE after THA or TKA. In that study, 180 patients were randomly divided into 3 groups, including 61 in aspirin group, 69 in LMWH group, and 60 in rivaroxaban group. The incidence of DVT in the 3 groups was 8.1%, 2.8%, and 5.0%, respectively.[26] These results showed the less effect of aspirin than LMWH and rivaroxaban in reducing the risk of DVT. Similar results were found by Zou, et al,[29] who carried out a RCT in China to compare aspirin with LMWH and rivaroxaban in prevention of DVT after TKA. They reported that the incidence of DVT was higher in aspirin group (16.36%, 18/110) than in rivaroxaban (2.94%, 3/102) and LMWH (12.5%, 14/112) groups.[29] These results confirmed that aspirin was inferior to rivaroxaban in preventing the risk of DVT.

There were several potential limitations in this study. First, the sample size varied greatly among the included studies, which ranged from 32 to 97,878. Studies with small sample size were more likely to produce an overestimated treatment effect as compared with larger trials. Second, the follow-up time in some of the included studies was less than 90 days, which would influence the effect evaluation of anticoagulants since VTE can be developed in 90 days postoperatively when no antithrombotic therapy is used.[7,8] Thus, results extracted from these studies would bias our pooled estimates. Third, due to the limited data, we could not perform subgroup analysis based on the surgical procedure to assess whether aspirin had better effect in THA than in TKA.

5. Conclusions

Our results suggested that aspirin and rivaroxaban offered similar effective in the prevention of VTE after TKA or THA. However, rivaroxaban seemed to have better effect than aspirin in reducing the risk of DVT, and aspirin was safer than rivaroxaban in decreasing the blood transfusion rate. Considering the potential limitations in this study, further large-scale and high-quality RCTs are needed to identify our findings.

Author contributions

LGP carried out the search and screening process, and YCZ&ZM assessment of study quality. LGP and XLC drafted the manuscript. LGP, YCZ, ZM, XLC, LHW, and TJL edited the manuscript. LGP and ZJM conceived the study, and LHW provided key expert input and editing throughout the process. TJL provided feedback on methodological and statistical aspects. All authors read and approved the final manuscript.

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