A comparison of aspirin against rivaroxaban for venous thromboembolism prophylaxis after hip or knee arthroplasty: A meta-analysis

Joshua Xu1, Aran Kanagaratnam1, Jacob Y Cao1,2, Gurpreet S Chaggar1 and Warwick Bruce1,3,4

Abstract

Purpose: Total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients are at an elevated risk of post-operative venous thromboembolism (VTE). Newer thromboprophylactic agents such as rivaroxaban are increasingly used and effective in preventing thromboembolic events but may worsen bleeding risk. Recent studies have suggested that the more cost-effective aspirin may also be effective in preventing VTE. This systematic review and meta-analysis aimed to compare the efficacy of aspirin against rivaroxaban for the prevention of VTE following TKA and THA. Methods: Electronic searches were performed using five databases from their date of inception to August 2018. Relevant studies were identified, with data extracted and meta-analyzed from the studies. Results: Five studies were included, which consisted of 2257 in the aspirin group and 2337 in the rivaroxaban group. There were no differences between aspirin and rivaroxaban for either VTE (p = 0.48) or its components deep vein thrombosis (p = 0.44) and pulmonary embolism (p = 0.98). Also, there were no differences between groups for either major bleeding (p = 0.17), any bleeding (p = 0.62), readmissions (p = 0.37) or wound complications (p = 0.17). Conclusion: Aspirin was not significantly different to rivaroxaban for prevention of VTE or adverse events after TKA or THA. However, this study was limited by the significant heterogeneity of the included studies. More large randomized studies are needed to add to this body of evidence.

Keywords
arthroplasty, aspirin, DVT, replacement, rivaroxaban, thromboembolism

Introduction

Patients undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA) face an elevated risk of post-operative venous thromboembolism (VTE). VTE, which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of post-operative morbidity and mortality. Without adequate prophylaxis, DVT can develop in up to 40–60% of post-operative patients, and fatal PE can reach 1–2%. Current guidelines suggest that prophylaxis should be given for a minimum of 10–14 days and should be strongly considered for up to 35 days.
The choice of prophylactic agent, though, remains controversial, and there is no current consensus regarding the preferred therapy. Commonly used agents include direct oral anticoagulants like rivaroxaban, a factor Xa inhibitor, and enoxaparin, a low molecular weight heparin. While effective, these medications have been shown to increase the bleeding risk, potentially increasing the risk of infection, prolonging recovery and increasing rates of readmission.4

The risk of VTE in post-TKA and post-THA patients has declined markedly with the advent of multidisciplinary care, changes in surgical technique and the preference for early physical therapy and ambulation.5 This has changed the risk–benefit analysis for prophylaxis agents, with some hypothesizing that any risk reduction from newer agents would be offset by an increased risk of bleeding complications.6 This has led to a renewed interest in aspirin, a cheap, generic anti-platelet drug. While there are multiple older studies evaluating its effectiveness, direct comparisons with newer agents within the modern clinical landscape have only recently begun appearing.7–9 We conducted a meta-analysis of studies comparing aspirin to rivaroxaban in patients after TKA or THA.

Methods

Literature search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this study. Electronic database searches were performed using PubMed, Ovid Medline, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials (CCTR), from their dates of inception to August 2018. The sensitivity of the search strategy was maximized by combining the terms ‘aspirin’ AND ‘rivaroxaban’ AND ‘arthroplasty OR replacement OR knee OR knee arthroplasty OR hip arthroplasty OR knee replacement OR hip replacement’ as the keywords when searching in the title, abstract, keywords and MeSH fields. The reference list of all retrieved articles was manually reviewed to further identify potentially relevant studies.

Selection criteria

Eligible studies for this systematic review and meta-analysis included patients receiving aspirin or rivaroxaban for chemoprophylaxis following knee or hip arthroplasty. Studies were included if they reported primary VTE outcomes or secondary outcomes (e.g. bleeding and wound complications) at follow-up. VTE included DVT and PE which was symptomatic or clinically detected. Bleeding was defined as major if it was fatal bleeding, symptomatic in a critical organ or region, or bleeding requiring reoperation. If an institution published duplicate studies with increased length of follow-up and accumulating patient numbers, the most recent data were used for quantitative analysis. All publications included were limited to those in the English language and involving human subjects. Conference presentations, case reports, reviews, editorials and expert opinions were excluded.

Data extraction and critical appraisal

All the relevant data were extracted from the article text, figures and tables. Two investigators (JX and GSC) independently reviewed and extracted data from the retrieved articles. Discrepancies between the two reviewers were resolved by discussion with senior authors to reach a consensus. The study characteristics extracted include study year, country, number of patients undergoing TKA and THA and number of patients receiving aspirin or rivaroxaban. The primary outcomes reported was any VTE, which included DVT and PE. Secondary outcomes included major bleeding, minor bleeding, readmission and wound complications. The risk of bias for all included studies was assessed according to the Cochrane Collaboration’s tool.

Statistical analysis

Outcomes were analyzed, with the relative risk (RR) or weighted mean difference used as the summary statistic. Random effects model was used in all cases regardless of the $I^2$ due to inherent heterogeneity between selected studies with regards to study design and patient demographics. Sensitivity analysis was performed by leave-one-out analysis. Publication bias was assessed by funnel plots. All statistical analysis was performed using Review Manager 5.3 software (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

Results

Quality of studies

A total of 1786 studies were identified by searching five electronic databases using our search strategy (Figure 1). By examining the study abstracts and removing duplicates, 1728 studies were excluded leaving 58 potentially relevant articles. Following the application of the inclusion criteria, a total of five studies were selected for quantitative analysis.10–14 These studies included a total of 4594 patients, with 2257 in the aspirin group and 2337 in the rivaroxaban group. From these patients, 2159 were THA and 2435 were TKA.

Of all the included studies, four studies were randomized controlled trials using prospectively collected data and one study was a retrospective observational study. The outcomes of the risk of bias assessment for these studies are summarized in Table 1. All studies had low or unclear risk of bias for random sequence generation, blinding of outcome assessment, incomplete outcome data and selective
reporting. In one study, there was a high risk of bias for allocation concealment and blinding of participants and personnel.

**Baseline characteristics**

The mean patient age in the aspirin group ranged from 62.7 to 71.2 years, compared to the rivaroxaban group which ranged from 62.7 to 67.1 years. For the aspirin group, 56.5% of the cohort were female and 56% of the rivaroxaban group were female. The mean body mass index (BMI) of the aspirin group ranged from 24.2 to 31.1 kg/m², compared to the rivaroxaban group which ranged from 24.6 to 31.0 kg/m². There were no significant differences between the aspirin and rivaroxaban groups with regards to age ($p = 0.25$), number of females ($p = 0.72$) and BMI ($p = 0.82$).

The dosage for aspirin ranged from 81 mg daily to 325 mg bi-daily. The dosage for rivaroxaban was 10 mg daily for all included studies. The duration of treatment for both aspirin and rivaroxaban ranged from 9 to 35 days. The follow-up time from the included studies ranged from 28 to 90 days. The study characteristics are summarized in Table 2.

**Operative details**

The mean operative blood loss in the aspirin group ranged from 130 to 314 mL, compared to the rivaroxaban group.

---

**Table 1.** Risk of bias assessment for included studies according to the Cochrane Collaboration’s tool.

| First author | Year | Random sequence generation | Allocation concealment | Blinding of participant and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting |
|--------------|------|-----------------------------|------------------------|--------------------------------------|------------------------------|------------------------|---------------------|
| Anderson     | 2018 | Low                         | Low                    | Low                                  | Low                          | Low                    | Low                 |
| Colleoni     | 2018 | Low                         | Unclear                | Unclear                              | Unclear                     | Low                    | Low                 |
| Lindquist    | 2018 | Unclear                    | Unclear                | Unclear                              | Unclear                     | Low                    | Low                 |
| Zou          | 2014 | Low                         | Unclear                | Unclear                              | Unclear                     | Low                    | Low                 |
| Jiang        | 2014 | Low                         | High                   | High                                 | Unclear                     | Low                    | Low                 |

---

**Figure 1.** PRISMA flow chart of systematic review and meta-analysis of aspirin versus rivaroxaban for venous thromboembolism prophylaxis after TKR or THA. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; THA: total hip arthroplasty.
which ranged from 171 to 354 mL. The mean operative time in the aspirin group ranged from 83 to 119 min, compared to the rivaroxaban group which ranged from 83 to 123 min. The mean length of hospital stay in the aspirin group ranged from 2.0 to 3.5 days, compared to the rivaroxaban group which ranged from 3.4 to 3.6 days. There were no significant differences between the groups for any of the operative characteristics.

**Assessment of VTE**

DVT was reported in four studies. No significant difference in DVT rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.67, 95% CI: 0.28–1.76, \( I^2 = 58\% , p = 0.44 \)) (Figure 2). PE was reported in two studies. No significant difference in PE rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.99, 95% CI: 0.38–2.59, \( I^2 = 0\% , p = 0.98 \)). Any VTE was reported in four studies, with similar VTE rates when comparing the rivaroxaban to the aspirin group (RR: 0.73, 95% CI: 0.31–1.75, \( I^2 = 60\% , p = 0.48 \)).

**Assessment of bleeding**

Major bleeding was reported in two of the studies. No significant difference in major bleeding was found when comparing the rivaroxaban to the aspirin group (RR: 0.39, 95% CI: 0.10–1.52, \( I^2 = 34\% , p = 0.17 \)) (Figure 3). Any bleeding was reported in two studies, with similar bleeding rates when comparing the rivaroxaban to the aspirin group (RR: 1.3, 95% CI: 0.45–3.79, \( I^2 = 81\% , p = 0.62 \)).

**Assessment of readmissions**

Readmissions were reported in two of the studies. No significant difference in readmission rate was found when comparing the rivaroxaban to the aspirin group (RR: 0.80, 95% CI: 0.50–1.30, \( I^2 = 0\% , p = 0.37 \)) (Figure 4).

**Assessment of wound complications**

Wound complications were reported in three studies. No significant difference in wound complication rate was found when comparing the rivaroxaban to the aspirin group (RR: 2.0, 95% CI: 0.73–5.55, \( I^2 = 0\% , p = 0.17 \)) (Figure 4).

**Discussion**

While TKA and THA are useful treatments that can offer patients significant increases in function and decreases in pain, they carry significant risk of VTE. Chemoprophylaxis is one prong of this strategy, along with multidisciplinary care and early mobilization. Both aspirin and rivaroxaban have been shown to be effective in reducing PE and DVT following TKR and THA. However, there is no published systematic review and meta-analysis comparing the outcomes of aspirin and rivaroxaban. Thus, the present study
aimed to determine whether the inexpensive, generic antiplatelet drug aspirin was comparable to the direct oral anticoagulant for VTE prophylaxis after TKA and THA.

There were no differences between aspirin and rivaroxaban for either VTE or its components DVT and PE. Similarly, there were no differences between groups for either major bleeding or any bleeding or for readmissions or wound complications. These results suggest that aspirin may be an appropriate choice of chemoprophylaxis agent after TKA and THA, given its lower cost and similar prophylactic and adverse event profiles.

While aspirin was superior to placebo in older trials investigating chemoprophylaxis after orthopaedic surgery, such as the Pulmonary Embolism Prevention Trial, this was in an era of higher VTE events. Additionally, 40% of the patients in the aspirin group received low molecular weight heparin. However, recently there have been more studies demonstrating the efficacy of aspirin for thromboprophylaxis. Along with that, in 2012, the American College of Chest Physicians and American Association of Orthopaedic Surgery now both recommend aspirin as a chemoprophylactic drug for VTE. Thus, with increasing support of the cheaper aspirin, the direct comparison to rivaroxaban, with all studies included in the meta-analysis from the past five years, is valuable.

The similarity in bleeding complications between aspirin and rivaroxaban is consistent with the results of other studies, which have found no differences in major bleeding or any bleeding or for readmissions or wound complications. While some studies have found a high risk of wound healing complication with rivaroxaban use, our study found no evidence of such an effect with aspirin.

Figure 2. Forest plot of DVT, PE and any VTE. DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

| Study name | Outcome | Risk ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|---------|------------|-------------|-------------|---------|---------|
| Anderson   | DVT     | 0.996      | 0.321       | 3.076       | -0.010  | 0.992   |
| Colleoni   | DVT     | 1.100      | 0.505       | 2.395       | 0.240   | 0.810   |
| Jiang      | DVT     | 0.180      | 0.055       | 0.592       | -2.822  | 0.005   |
| Zou        | DVT     | 0.696      | 0.275       | 1.760       | -0.766  | 0.443   |

| Risk ratio and 95% CI |
|-----------------------|
| 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |
| Favours Rivaroxaban   | Favours Aspirin     |

| Study name | Outcome | Risk ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|---------|------------|-------------|-------------|---------|---------|
| Anderson   | PE      | 1.136      | 0.413       | 3.126       | 0.247   | 0.805   |
| Colleoni   | PE      | 0.263      | 0.012       | 6.009       | -0.836  | 0.403   |
|           |         | 0.989      | 0.378       | 2.591       | -0.022  | 0.982   |

| Risk ratio and 95% CI |
|-----------------------|
| 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |
| Favours Rivaroxaban   | Favours Aspirin     |

| Study name | Outcome | Risk ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|---------|------------|-------------|-------------|---------|---------|
| Anderson   | Any VTE | 1.085      | 0.480       | 2.451       | 0.195   | 0.845   |
| Colleoni   | Any VTE | 1.556      | 0.156       | 15.463      | 0.377   | 0.706   |
| Jiang      | Any VTE | 1.100      | 0.505       | 2.395       | 0.240   | 0.810   |
| Zou        | Any VTE | 0.180      | 0.055       | 0.592       | -2.822  | 0.005   |
|           |         | 0.733      | 0.308       | 1.745       | -0.702  | 0.482   |

| Risk ratio and 95% CI |
|-----------------------|
| 0.1 | 0.2 | 0.5 | 1 | 2 | 5 | 10 |
| Favours Rivaroxaban   | Favours Aspirin     |
difference in wound complications between the aspirin and rivaroxaban group.\textsuperscript{17,18}

The key strengths of the present analysis are that the studies included directly compared rivaroxaban to aspirin, and there were no significant differences between groups on either patient characteristics or operative characteristics. Four of the five studies included were randomized controlled trials. The studies included were also all recent

\begin{figure}
\centering
\includegraphics[width=\textwidth]{forest_plot}
\caption{Forest plot of major bleeding and any bleeding.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{forest_plot}
\caption{Forest plot of readmission and wound complications.}
\end{figure}
studies, which contributes to the current clinical relevance of these findings. While the findings from this study are comparable to Anderson et al., we pooled the patient cohort from five studies to increase the power of these findings. Along with that this is the first meta-analysis comparing aspirin to rivaroxaban for thromboprophylaxis following TKA or THA.

There are several limitations to this systematic review and meta-analysis. The primary limitation of this analysis is that the majority of patients came from two studies. There was significant heterogeneity in the outcome which could have stemmed from difference in study protocols. For example, in the large randomized trial by Anderson et al., all patients received 5 days of rivaroxaban before being randomized to aspirin or rivaroxaban. In the study by Jiang et al., the rivaroxaban group received 5 days of low molecular weight heparin before being switched to rivaroxaban, while the aspirin group was started on aspirin from day 1. In the other studies, patients were started on aspirin or rivaroxaban from day 1. While the dosage of rivaroxaban was the same in all studies, aspirin dosage varied from 81 mg daily to 325 mg bi-daily. Further, the duration of prophylaxis varied between 9 and 35 days, though this was kept consistent between subgroups within the original studies.

This meta-analysis also does not address the efficacy of these chemoprophylaxis regimens in high-risk populations, for example, people with cancer or previous VTE. This is because relatively small numbers of these patients were enrolled in the included studies, and none reported the specific outcomes for these subgroups. Thus, chemoprophylaxis efficacy in high-risk subgroups remains an open question for future research.

Conclusion
The present systematic review and meta-analysis found that aspirin was not significantly different to rivaroxaban for prevention of VTE or adverse events after TKA or THA. More large randomized studies are needed to add to this body of evidence.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Joshua Xu https://orcid.org/0000-0001-7598-6482

References
1. Quinlan DJ, Eikelboom JW, Dahl OE, et al. Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. J Thromb Haemost 2007; 5: 1438–1443.
2. Howie C, Hughes H and Watts AC. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. J Bone Joint Surg Br 2005; 87: 1675–1680.
3. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141: e278S–e325S.
4. Parvizi J, Ghanem E, Joshi A, et al. Does ‘excessive’ anticoagulation predispose to periprosthetic infection? J Arthroplasty 2007; 22: 24–28.
5. Bozic KJ, Vail TP, Pekow PS, et al. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? J Arthroplasty 2010; 25: 1053–1060.
6. Lotke PA and Lonner JH. The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. Clin Orthop Relat Res 2006; 452: 175–180.
7. Harris WH, Salzman EW, Athanasoulis CA, et al. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med 1977; 297: 1246–1249.
8. McKenna R, Bachmann F, Kaushal SP, et al. Thromboembolic disease in patients undergoing total knee replacement. J Bone Joint Surg Am 1976; 58: 928–932.
9. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355: 1295–1302.
10. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med 2018; 378: 699–707.
11. Jiang Y, Du H, Liu J, et al. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. Chin Med J 2014; 127: 2201–2205.
12. Colleoni JL, Ribeiro FN, Mos PAC, et al. Venous thromboembolism prophylaxis after total knee arthroplasty (TKA): aspirin vs. rivaroxaban. Rev Bras Ortop 2018; 53: 22–27.
13. Lindquist DE, Stewart DW, Brewster A, et al. Comparison of postoperative bleeding in total hip and knee arthroplasty patients receiving rivaroxaban, enoxaparin, or aspirin for thromboprophylaxis. Clin Appl Thromb Hemost 2018; 24(8): 1315–1321.
14. Zou Y, Tian S, Wang Y, et al. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. Blood Coagul Fibrinolysis 2014; 25: 660–664.
15. An VV, Phan K, Levy YD, et al. Aspirin as thromboprophylaxis in hip and knee arthroplasty: a systematic
review and meta-analysis. *J Arthroplast* 2016; 31: 2608–2616.

16. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358: 2776–2786.

17. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, et al. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ* 2012; 344: e3675.

18. Jameson SS, Rymaszewska M, Hui AC, et al. Wound complications following rivaroxaban administration: a multicenter comparison with low-molecular-weight heparins for thromboprophylaxis in lower limb arthroplasty. *J Bone Joint Surg Am* 2012; 94: 1554–1558.