Effectiveness and safety of rivaroxaban for the prevention of thrombosis following total hip or knee replacement

A systematic review and meta-analysis

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Abstract

Background: Prophylactic anticoagulant therapy is recommended to reduce the risk of venous thromboembolism (VTE) after total hip or knee arthroplasty, and has become the standard of care. Rivaroxaban is a novel oral medication that directly inhibits factor Xa for the prevention and treatment of thromboembolic conditions.

Method: A meta-analysis of randomized controlled trials (RCTs) was performed to determine the efficacy and safety of rivaroxaban after total hip arthroplasty (THA) and total knee arthroplasty (TKA) surgery. We reviewed several databases including PubMed, the Cochrane Library, Embase and the US trial registry to detect appropriate RCTs for our meta-analysis. The primary efficacy outcome of this meta-analysis was the combination of any deep-vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and death from any cause. The main safety outcome was bleeding events which included significant bleeding events, clinically relevant insignificant bleeding events, or minor events. Other end points were the number of patients who received blood transfusion the volume of transfused whole blood or red blood cells, and the volume of postoperative drainage.

Result: Thirteen RCTs were included in this meta-analysis. This meta-analysis showed that the overall rate of VTE events, DVT, PE, and death were 1%, 6%, <1% and <1%, respectively, for patients receiving treatment with rivaroxaban after THA and TKA surgery. The subgroup analysis demonstrated rivaroxaban had more superior effects in THA patients. The pooled analysis of bleeding events showed that the overall rate of major bleeding events, overt bleeding events associated with fall in Hb of >2 g/DL, clinically overt bleeding events leading to transfusion of >2 units of blood, clinically overt bleeding events leading to further surgeries, and non-major bleeding events were <1%, <1%, <1%, <1%, and 3%, respectively.

Conclusion: This is the first systematic review of the literature providing incidence of efficacy and safety outcomes for thromboprophylaxis in THA and TKA patients. Moreover, this meta-analysis showed that rivaroxaban had more superior effect in THA patients.

Abbreviations: ACCP = American college of chest physicians, DVT = deep vein thrombosis, NOAs = novel oral anticoagulants, PE = pulmonary embolism, RCTs = randomized controlled trials, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

Keywords: meta-analysis, rivaroxaban, total hip arthroplasty, total knee arthroplasty, venous thromboembolism
1. Introduction

Venous thromboembolism (VTE) is a life-threatening complication after major orthopedic surgeries such as total knee arthroplasty (TKA) or total hip arthroplasty (THA) and may be associated with deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] In the absence of thromboprophylaxis, the incidences of DVT can be as high as 42% to 57% and 40% to 80% following THA[2,3] and TKA[1], respectively. The risk of deadly PE for patients undergoing THA surgery patients without thromboprophylaxis is 0.1% to 2% and it is one of main causes of perioperative mortality.[2] Similarly, non-fatal and fatal PE occurred in 1.8% to 7.0% and 0.2% to 0.7% of cases receiving TKA.[2]

Minimizing the incidence of VTE and associated complications, such as PE, remains an important clinical burden following orthopedic surgeries.[6,7] Prophylactic anticoagulant therapy is recommended to reduce the risk of VTE after total hip or knee arthroplasty, and has become the standard of care.[8] However, this therapy brings about debate as effective therapy for VTE also simultaneously increase the risk of bleeding events. Bleeding is a cause for significant concern in orthopedic surgeons who prescribe pharmacological prophylactic anticoagulants, though the full clinical impact of VTE and its status as a leading cause of preventable death in hospitals continues to be underestimated. There is an increasing interest in developing new drugs and treatment modalities.

Novel oral anticoagulants (NOACs) are now widely available and have stable and predictive pharmacokinetic and pharmacodynamic profiles. In 2001, Rivaroxaban, an oral direct inhibitor of factor Xa, was approved by the food and drug administration for the prevention of VTE in adults undergoing THA or TKA surgery in the United States.[9] Recent dose-finding studies in patients undergoing major orthopedic surgery showed dose-response effect of rivaroxaban and indicated that rivaroxaban at a dose of 10 mg once daily had sufficient efficacy and safety in phase III trials.[10-14]

Systemic reviews and meta-analyses have compared the efficacy and safety of rivaroxaban with other anticoagulation agents in THA and TKA.[15-18] However, the doses of rivaroxaban were variable among studies. Most of the existing meta-analyses did not limit doses and compare different efficacy of rivaroxaban in TKA and THA. Moreover, Phase III studies showed that a 10 mg dose of rivaroxaban once daily had adequate efficacy and safety to merit further investigation.[13] To date, 13 randomized controlled trials (RCTs) have been carried out to compare the efficacy and safety of rivaroxaban in TKA and THA patients.[10-13,18-21] The evidence from these RCTs seemed to support the use of rivaroxaban for the prevention of VTE after TKA, however, it was inconclusive due to the small sample size. Moreover, broad comparisons of medication doses in prior studies are inadequate. Therefore, the aim of the current study is to better illuminate the efficacy and safety of rivaroxaban at a dose of 10 mg once daily for the prevention of thrombotic events following total hip or knee arthroplasty by performing a meta-analysis of 13 relevant RCTs.

2. Methods

2.1. Data sources

This systematic review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] We searched the database of PubMed (up to June 2017), the Cochrane Library (up to June 2017), Embase (1947 to June 2017), and the US trial registry (www.ClinicalTrials.gov) to identify relevant RCTs for our meta-analysis. The search was restricted to RCTs and limited to English publication. We used the following MESH terms/keywords: “rivaroxaban”, “total knee arthroplasty”, “total hip arthroplasty”, “thromboprophylaxis”, “venous thromboembolism”, “clinical studies” and these similar items. In addition, reference lists of eligible articles were screened for additional articles. Only publications with original data from clinical studies were included. Publications reporting pooled analysis of data or meta-analysis of rivaroxaban were excluded.

2.2. Study selection

The studies were reviewed by 2 independent reviewers who screened the titles and abstracts in order to evaluate the contents of potentially eligible studies. Disagreements were resolved by a consensus vote. The eligibility criteria for inclusion in the meta-analysis were:

1. RCTs that reported the efficacy and safety of rivaroxaban (with approved doses of 10 mg) for thromboprophylaxis;
2. the study included patients of all ages undergoing total hip or knee replacement;
3. the study provided efficacy/safety information including; any DVT diagnosed by venography, PE, major bleeding or hemorrhage (as defined by the investigators). Both blinded and unblinded studies were included; abstracts in scientific conferences were not included. The studies that were excluded include meta-analyses on factor Xa inhibitor or systemic reviews without statistical analysis, and experimental trials and trials focusing on rivaroxaban pharmacokinetic or pharmacodynamics variables.

2.3. Data extraction

For the included studies, 2 investigators independently carried out the data extraction and moved it into Microsoft Excel 2010 within duration of 2 weeks without notifying each other until both of their tasks were completed. A predesigned review form was initially used to extract the following information: study characteristics (methodology, type of surgery, study design and drugs, and publication details), participants (sample size, sex, age, interventions (dose, duration, and administration), and outcomes (efficacy and safety outcomes).

2.4. Analyzed outcomes

The chief efficacy outcome of this meta-analysis was the amalgamation of any DVT, non-fatal PE, and death from any cause during therapy. Most of the RCTs recruited also noted secondary efficacy outcomes. The secondary efficacy outcome in this review was major VTE, which was defined as the combination of proximal DVT, non-fatal PE, and VTE related death.

The key safety outcome of the meta-analysis was bleeding events which included major bleeding events, clinically significant non-major bleeding events, or minor events. A major bleeding event was defined as bleeding that was fatal, that occurred in a critical organ, or that required additional surgeries, or clinically overt bleeding associated with a drop in the hemoglobin level of at least 2 g/dL or resulted in the transfusion of ≥ 2 units of blood. Other end points were the number of patients who received blood transfusion the volume of transfused whole blood or red blood cells, and the volume of postoperative drainage.

2.5. Data analysis

Statistical analyses were performed with the Review Manager 5.2 version software (Cochrane Library Software, Oxford, UK) and
Stata version 12.0 (Stata Corp, College Station, TX). The heterogeneity across studies’ effects was calculated by Cochran $Q$ test and the $I^2$ measure of inconsistency. In this study, we used $I^2$ to measure heterogeneity. For each study, we assessed the relative risk (RR) and the corresponding 95% confidence intervals (CI) of efficiency and safety events. The pooled RR with 95% CI was summarized to represent the total effect size. The fixed effects model was selected for the homogeneous outcomes ($P > .1$ and $I^2 < 40\%$) and the random effects model was applied for heterogeneous outcomes ($P < .1$ or $I^2 \geq 40\%$). Publication bias was assessed graphically with funnel plots. Based on the type of surgery (THA or TKA), we conducted subgroup analyses for the primary outcomes.

3. Results

3.1. Study selection process

The meticulous screening and selection method is shown in Fig. 1. The search was performed in PubMed, the Cochrane Library,
### Table 1

Main characteristics of the trials included in the meta-analysis.

| Study                | Type of study                  | Follow up (days) | Dose times Rivaroxaban (mg) | Type of surgery | Surgery duration (min) | No. of patients in Rivaroxaban (10 mg) group | Female (%) | Mean age (years) | Mean weight (kg) | BMI (kg/m²) | No. of patients For primary efficacy analysis |
|----------------------|--------------------------------|------------------|-----------------------------|----------------|------------------------|-----------------------------------------------|------------|-----------------|-----------------|------------|--------------------------------------------|
| 1 Turpie et al. (2005) | Multicenter, double-blind, RCT | 30 bid           | 190                         | TKA            | 88                     | 103                                           | 64         | 67              | 86.4±19         | 31.8±6.3   | 60                                                        |
| 2 Eriksson et al. (2006) | Multicenter double-blind RCT | 30-60 once daily | 120                         | THA            | 89                     | 142                                           | 63         | 64              | 75.6           | 26.9       | 113                                                       |
| 3 Eriksson et al. (2006) | Multicenter double-blind RCT | 30-60            | 120                         | bid            | 85                     | 133                                           | 60         | 65              | 77             | 27         | 101                                                       |
| 4 Eriksson et al. (2007) | Multicenter open-label RCT   | 30-60 bid        | 120                         | THA            | 68                     | 65                                            | 65         | 76              | 27             | 27         | 55                                                        |
| 5 Kakkar et al. (2008) | Multicenter double-blind RCT | 30-42            | 120                         | THA            | 95                     | 1228                                          | 54.3       | 61.4            | 74.3           | 26.4       | 864                                                       |
| 6 Eriksson et al. (2008) | Multicenter double-blind RCT | 30-35            | 120                         | THA            | 90.6                   | 2209                                          | 55.2       | 63.1            | 78.1           | 27.8       | 1595                                                      |
| 7 Lassen et al. (2008) | Multicenter double-blind RCT | 30-35            | 120                         | TKA            | 96.4                   | 1220                                          | 70.2       | 67.6            | 80.1           | 25.9       | 824                                                       |
| 8 Turpie et al. (2009) | Multicenter double-blind RCT | 30-35            | 120                         | TKA            | 100.4                  | 1526                                          | 66         | 64.4            | 84.7±20.4      | 30.9±6.2   | NA                                                       |
| 9 Zou et al. (2014) | Non-multicenter double-blind RCT | 28               | 80                          | TKA            | 102                    | 68.6                                         | 63.5       | NA              | 27             | 102        | 102                                                      |
| 10 Yi et al. (2014) | Non-multicenter double-blind RCT | 40               | 120                         | TKA            | 90                     | 60                                            | 93.3       | 63.8            | 4.6±3.6        | 60         | 60                                                        |
| 11 Öder et al. (2015) | Non-multicenter Non-blinded RCT | 42               | 120                         | TKA/THA        | 90                     | 60                                            | 71.67      | 65              | NA             | NA         | NA                                                        |
| 12 Benedetto et al. (2016) | Non-multicenter double-blind RCT | 30               | 120                         | TKA            | 38                     | NA                                           | NA         | NA              | NA             | NA         | NA                                                        |
| 13 Liu et al. (2017) | Non-multicenter double-blind RCT | 9                | 120                         | TKA/THA        | 60                     | NA                                           | NA         | NA              | NA             | NA         | NA                                                        |

DVT = deep vein thrombosis, PE = pulmonary embolism, RCT = randomized controlled trials, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

Embase, and Clinical trials. The 580 publications were included by primary searching. After the removal of duplicates using Endnote software and manual confirmation, 383 publications lacking duplications remained. The 346 studies were excluded because they were reviews, case reports, meeting records, and irrelevant or incomplete data. Only 37 articles met the eligibility criteria after screened by title and abstract review. After we verified the full text of the remaining 37 articles, 24 studies were discarded. We eventually identified 13 RCTs that satisfied all of the criteria for inclusion in the meta-analysis. No additional eligible articles were obtained via screening the reference lists of identified primary studies.

### 3.2. Study characteristics

The chief study features of the 13 included RCTs [10–13,19–27] (type of study, baseline characteristics of the included population, type of surgery, surgery duration, and number of patients for efficacy and safety analysis) are shown in Table 1. Within the included RCT studies, a total of 6949 patients were randomized to the rivaroxaban therapy. The number of patients evaluating efficacy and safety outcomes are inconsistent, so we presented specific number of patients respectively. In an effort to avoid clinical heterogeneity, only the group treated with a total dose of 10 mg daily was included for dose-ranging studies. For the patients included in our meta-analysis, rivaroxaban was dosed...
orally twice per day with a total daily dose of 10 mg in three RCTs, and orally once daily with a dose of 10 mg in the other 10 RCTs. All of the trials were reported in English between 2005 and 2017. They included patients with a mean age between 61 and 68 years old. There were a high proportion of females, ranging from 54% to 93%. Of the 13 RCTs, 6 included patients that underwent THA,\[2,5,7,9,12,18\] 5 included patients that underwent TKA,\[11,13,17,23,24\] and 2 included patients that underwent either a THA or a TKA.\[25,27\] All of the included RCTs were assessed to be good in terms of methodology (10 trials with appropriate multicenter and double blinding protocols).

3.3. Efficacy outcomes

The date on major VTE events were provided in 9 relevant RCTs.\[5–7,9,12,13,18,21\] The overall rate of major VTE was 1%; random-pooled. Separate effect model 0.01 (95% CI: 0, 0.01; \(I^2 = 56.8\%\); \(P = .018\)) (Fig. 2A). Analyses of the total hip and knee arthroplasty subgroups showed the pooled rate of VTE was < 0.01 (95% CI: 0, 0.01; \(I^2 = 31.6\%\); \(P = .211\)) (Fig. 5A) and 1% (95% CI: 0, 0.01; \(I^2 = 14\%\); \(P = .385\)) (Fig. 5A) respectively. The results were similar to those of the overall meta-analysis. Pooled analysis of all 11 relevant RCTs demonstrated that the incidence of DVT was 6% (95% CI: 0.04, 0.09; \(I^2 = 93.3\%\); \(P < .0001\)) (Fig. 2B). With regards to the THA subgroup, the overall incidence of DVT was 4% (95% CI: 0.02, 0.06; \(I^2 = 86.9\%\); \(P < .001\)) which was lower than that in TKA subgroup and the overall group (Fig. 5B). In the TKA subgroup, there was higher total DVT 8% (95% CI: 0.04, 0.11; \(I^2 = 85.2\%\); \(P < .001\)) than that in THA subgroup and the overall group (Fig. 5B). Nine studies\[5–7,9,12,13,18,21\] including 6889 participants in rivaroxaban group reported data on PE. By meta-analysis, the rate of PE was less than 1% (95% CI: 0, < 0.01; \(I^2 = 0\%\); \(P = .764\)) (Fig. 2C). Overall rate of death from 10 of 13 RCTs studies was < 0.01 (95% CI: 0, < 0.01; \(I^2 = 0\%\); \(P = .922\)) (Fig. 2D).

3.4. Safety outcomes

We performed pooled analyses of bleeding events to evaluate the safety of rivaroxaban. Eight RCTs\[5–7,9,12,13,18,21\] were included into the meta analysis model of major bleeding events (Fig. 3A). The overall response rate of major bleeding was less than 0.01 (95% CI: 0, < 0.01; \(I^2 = 57.6\%\); \(P = .211\)). Eight RCTs\[5–7,9,12,13,18,21\] provided clinically overt bleeding events. Meta-analysis of the 8 studies revealed an overall incidence of overt bleeding events associated with fall in Hb of > 2g/DL was < 0.01 (95% CI: 0, < 0.01; \(I^2 = 0\%\); \(P = .745\)) (Fig. 3B). The total rate of the clinically apparent bleeding events prompting transfusion of > 2 units of blood was < 0.01 (95% CI: 0, < 0.01; \(I^2 = 0\%\); \(P = .444\)) (Fig. 4A) and the overall rate of clinically overt bleeding events leading to re-operation was < 0.01 (95% CI: 0, < 0.01; \(I^2 = 19.5\%\); \(P = .275\)) (Fig. 4B). A meta-analysis was performed for
synthesis of data from 8 of the 13 studies to estimate the incidence of non-major and clinically relevant bleeding events. It reported that the rate of minor bleeding events was 3% (95% CI: 0.02, 0.04; $I^2 = 81.7\%$; $P < .01$) (Fig. 4D). Meta-analysis of the above 8 studies also showed the total proportion of patients receiving blood transfusions was 51% (95% CI: 0.44, 0.58; $I^2 = 96.3\%$; $P < .01$) (Fig. 4C).

3.5. Publication bias

In the pooled evaluation of efficacy and safety of rivaroxaban in THA and TKA patients, there was no publication bias due to the funnel plot (Fig. 6). Sensitivity analyses were used to validate the strength of the strategy through the incidence of efficacy outcomes in these patients. It was shown that there was no dramatic change in the findings for the review overall (Fig. 7).
4. Discussion

In the current study, we carried out meta-analyses to evaluate the effectiveness and safety of rivaroxaban (dose of 10 mg) for thromboprophylaxis in THA and TKA patients. This is the first known meta-analyses of the existing literature to determine the rate of efficacy and safety outcomes in these patients. As such, it provides novel information for the gap in the literature.

The evidence-based guidelines put forth by the American College of Chest Physicians (ACCP) recommend extensive prophylaxis against VTE for patients undergoing total hip or knee replacement.\cite{30,31} Patients are usually required to continue taking anticoagulants following hospital discharge, but the brevity of present-day stays in the hospital often result in a lesser number of patients receiving the adequate amount of prophylaxis recommended by the clinical guidelines.\cite{30,31} Traditional anticoagulant treatments have their limitations in clinical use. This has strongly encouraged the development of NOACs.\cite{32}

Several previous systematic reviews have compared the efficacy and safety of oral rivaroxaban and subcutaneous enoxaparin for
the prevention of VTE after total knee replacement.\cite{16-18,33} However, most of these studies included all of the rivaroxaban dosages and did not select a certain dosage. Recent dose-finding studies support that rivaroxaban at a dose of 10mg once daily had sufficient efficacy and safety after major orthopedic surgery in phase III trials.\cite{10,11,13,14} In contrast to these earlier pooling analysis,\cite{16-18,33} we selected the recommended dosage of rivaroxaban (10mg) in 13 RCTs which have more universality and presented more guiding significance for clinical practice. A previous meta-analysis comparing the efficacy and safety of rivaroxaban versus enoxaparin included only the group treated with 10mg rivaroxaban.\cite{15} It was worth to mention that our meta-analysis included 5 more clinical trials, which enhanced the statistical reliability. Five above mentioned previous systematic reviews only compared the efficacy or safety of rivaroxaban with other anticoagulants but did not clarify the incidence of relevant outcomes which propelled us to do this study.

This comprehensive meta-analysis of 13 studies showed that the overall rate of major VTE events, DVT, PE, and Death were 1%, 6%, <1%, and <1% respectively for patient receiving treatment of rivaroxaban after THA and TKA surgery. The separate analyses of the total hip and knee arthroplasty subgroups revealed that rivaroxaban was more effective in THA patients than in TKA patients in terms of the rate of VTE, although the difference was not statistically significant. The meta-analysis also showed that the overall incidence of DVT was significantly lower in THA subgroup than that in TKA subgroup and the overall group. In other words, the subgroup analysis demonstrated rivaroxaban had more superior effect for thromboprophylaxis when used in THA patients.

The pooled analyses of bleeding events showed that overall rate of major bleeding events, overt bleeding events associated with fall in Hb of >2 g/DL, clinically overt bleeding events leading to transfusion of >2 units of blood, clinically apparent bleeding events leading to further operations, and non-major bleeding events were <1%, <1%, <1%, <1%, and 3% respectively. The safety outcome investigation also revealed that the total proportion of patients receiving blood transfusions was 51%. These results demonstrated that rivaroxaban has good safety for thromboprophylaxis when used in arthroplasty surgery patients.

5. Conclusions

This meta-analysis showed that the overall rate of major VTE events, DVT, PE, and death were 1%, 6%, <1%, and <1%, respectively, for patients receiving treatment with rivaroxaban after THA and TKA surgery. It also showed that the overall rate of major bleeding events, overt bleeding events associated with fall in Hb of >2 g/DL, clinically overt bleeding events leading to transfusion of >2 units of blood, clinically apparent bleeding events leading to further surgeries, and non-major bleeding events were <1%, <1%, <1%, <1%, and 3%, respectively. This is the first systematic review of the literature providing incidence of efficacy and safety outcomes for thromboprophylaxis in THA and TKA patients. Moreover, this meta-analysis showed that rivaroxaban had more superior effect for thromboprophylaxis when used in THA patients.

Supporting information: S1 Table, http://links.lww.com/MD/C842. The PRISMA checklist.
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