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PHARMACODYNAMICS

Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials

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Abstract
Purpose Rivaroxaban is a newly developed oral medicine that direct inhibits factor Xa for the prevention and treatment of thromboembolic disorders. The objective of this study was to compare the efficacy and safety of rivaroxaban versus enoxaparin, a medicine routinely used for thromboprophylaxis after total hip or knee arthroplasty.
Methods We performed a meta-analysis of relevant randomized controlled trials (RCTs) identified in PubMed, Cochrane library, and Embase. The primary efficacy outcome for our meta-analysis was total venous thromboembolism (VTE) and all-cause mortality. The primary safety outcome was bleeding events, which were categorized as major, clinically relevant non-major, or minor events.
Results Eight RCTs, involving 15,586 patients, were included in our meta-analysis. Compared to enoxaparin, thromboprophylaxis with rivaroxaban was associated with significantly fewer VTE and all-cause mortality [9,244 patients, risk ratio (RR) 0.56, 95% confidence interval (CI) 0.39–0.80] cases and a similar incidence of bleeding cases (major bleeding events: 13,384 patients, RR 1.65, 95% CI 0.93-2.93; clinically relevant non-major bleeding events: 13,384 patients, RR 1.21, 95% CI 0.98–1.50; total bleeding events, 13,384 patients, RR 1.10, 95% CI 0.97–1.24). The total hip or knee arthroplasty subgroup analysis revealed consistent efficacy and safety findings.
Conclusions Rivaroxaban was more effective than the recommended dose of enoxaparin and had a similar safety profile for thromboprophylaxis after hip and knee arthroplasty.

Keywords Embolism · Thrombosis · Prophylaxis · Anticoagulants · Meta-analysis

Background

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Methods

Data sources

The study was performed using a prespecified search strategy and study eligibility criteria. We performed an extensive search of PubMed (up to March 2010), the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2010), and Embase (1980 to March 2010) to identify relevant RCTs for our meta-analysis. We restricted the search to RCTs. Search term combinations were "rivaroxaban", "enoxaparin", "low-molecular-weight heparins", "total knee arthroplasty" and similar, "total hip arthroplasty" and similar, "thromboprophylaxis" and similar, and "venous thromboembolism" and similar. The language of the research papers was not restricted to English. All reference lists from the relevant articles and reviews were hand searched for additional eligible studies. Experts in the field were also consulted. The articles that were not available to us were requested from the authors.

Study selection

Two reviewers (YBC and JDZ) independently searched the literature and examined relevant RCTs for further assessment. The criteria for including a study in our meta-analysis was: (1) it was a RCT; (2) it included patients of all ages undergoing total hip or knee arthroplasty; (3) it compared the efficacy and safety of rivaroxaban versus enoxaparin for thromboprophylaxis. Trials with a blinded and unblinded design were both included; abstracts in scientific conferences were not included. Experimental trials and trials focusing on pharmacokinetic or pharmacodynamic variables were excluded.

Qualitative assessment

Evaluation of the methodological quality of the RCTs included in the meta-analysis was performed independently by the two reviewers (MMA and ZZ) using the Jadad scoring system as follows [18]. One point is awarded for the presence of randomization, blinding, and data on study withdrawals, respectively. Also, if the randomization or blinding procedures are appropriate, one point is awarded for each procedure; no points are awarded if no data are provided on the methodology of the above-mentioned procedures. Finally, if any of these procedures is not deemed appropriate, one point is deducted for each one. The maximum score that can be attributed to an RCT is 5. An RCT with a score >2 is considered to be an RCT of adequately good quality [19, 20].

Data extraction

The two reviewers (YBC and JDZ) independently extracted data from the included trials. Data were extracted from each study with a predesigned review form. In the case of disagreement between the two reviewers, a third reviewer extracted the data, and the results were attained by consensus. We contacted the authors of trials for missing data when necessary. Data on study characteristics (methodology, included population, study design and drugs, and publication details), endpoint data (efficacy outcomes and safety outcomes), and adverse events during treatment and follow up were extracted.

Analyzed outcomes

The primary efficacy outcome of this meta-analysis was total VTE and all-cause mortality, defined as the composite of VTE (any deep-vein thrombosis or nonfatal pulmonary embolism) and death from any cause. The secondary efficacy outcome included major VTE (defined as the composite of proximal deep vein thrombosis, nonfatal pulmonary embolism, or death from VTE), deep vein thrombosis (any thrombosis, including both proximal and distal), and symptomatic VTE.

The primary safety outcome of the meta-analysis was bleeding events, which were categorized as major events, clinically relevant non-major bleeding events, or minor events, beginning after the first dose of the study drug and remaining up to 2 days after the last dose of the study drug. A major bleeding event was defined as bleeding that was fatal, that occurred in a critical organ,

or that required a re-operation, or as extrasurgical-site bleeding that was clinically overt and associated with a fall in the hemoglobin level of at least 2 g/dl or that required the transfusion of ≥2 U of whole blood or packed cells. The secondary safety outcome was drug-related adverse event.

Data analysis and statistical methods

Statistical analyses were done with Review Manager ver. 5.0.20 (Cochrane Collaboration, Oxford, UK). We assessed the heterogeneity of the trial results by calculating a chi-square test of heterogeneity and the I^2 measure of inconsistency. The publication bias was assessed by examining the funnel plot. We used a random-effects model by using the DerSimonian and Laird method for pooling risk ratios (RRs) and 95% confidence intervals (CIs) of all primary and secondary outcomes throughout the meta-analysis. Heterogeneity was investigated through subgroup analyses as defined above.

Results

Study selection process

The flow diagram (Fig. 1) shows the detailed screening and selection process that we applied before including trials in our meta-analysis. The search was performed in PubMed, the Cochrane Central Register of Controlled Trials, and Embase. We obtained 18 full papers from 84 studies for detailed evaluation. We ultimately identified eight RCTs that fulfilled all of the criteria for inclusion in the meta-analysis.

Study characteristics

The main characteristics of the eight included RCTs (type of study design, characteristics of the included population, drug tested, number of patients randomized, and Jadad score) are presented in Table 1. The total population of the included trials was 15,586 patients. All of the included RCTs were performed exclusively in adult patients undergoing total hip arthroplasty (five RCTs) or knee arthroplasty (three RCTs), and all RCTs were assessed to be good in terms of methodology (seven trials with appropriate double blinding and double-dummy protocols). The high Jadad scores (Five RCTs had a score of 5, two had 4, and one had 3) also indicated the high quality of the RCTs included in the meta-analysis. We examined the funnel plot [standard error (SE) of log RR plotted against RRs] to estimate publication bias and obtained a symmetric inverse funnel distribution.

Treatment schedules for thromboprophylaxis were comparable between the included trials. All of the patients in the rivaroxaban group received the first dose after 6–8 h of wound closure. For dose-ranging studies, only the group treated with a total daily dose of 10 mg was included in the analysis to avoid clinical heterogeneity. In the patients included in our meta-analysis,

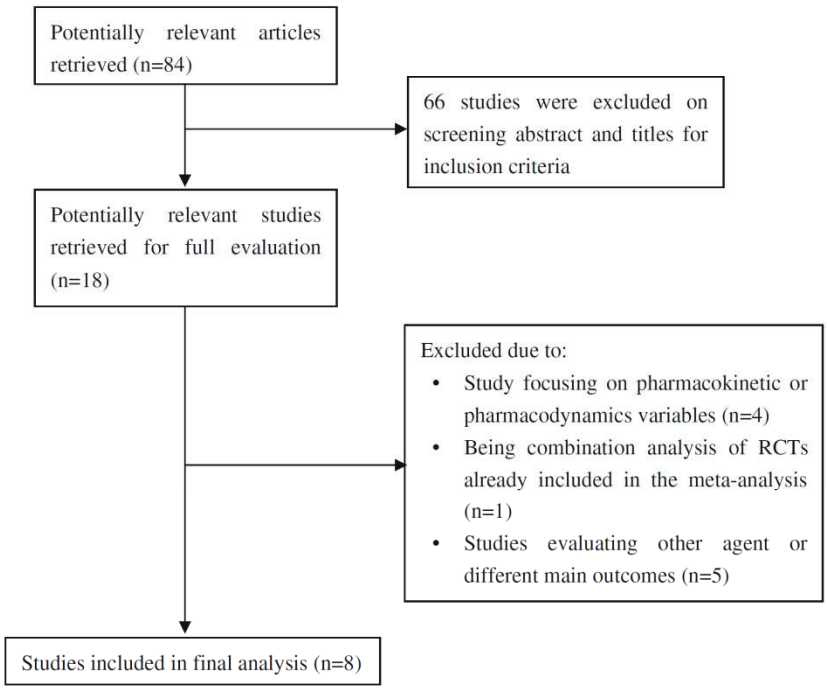

Fig. 1 Flow diagram of the randomized controlled trials (RCTs) reviewed

Table 1 Main characteristics of the trials included in the meta-analysis

Study	Type of study	Included population	Drug tested		Number of patients randomized	Jadad score
			Rivaroxaban	Enoxaparin		

RCT, Randomized controlled trial

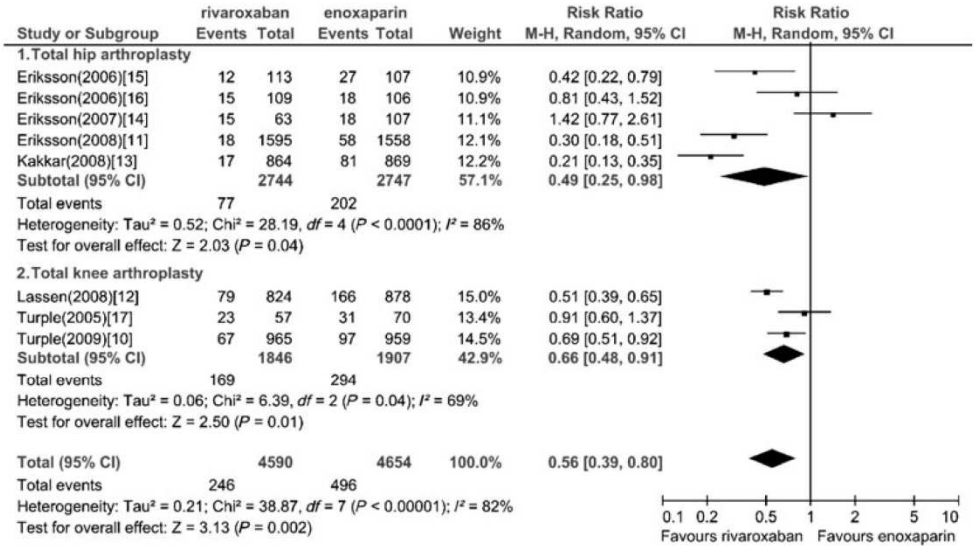

Fig. 2 Meta-analyses of the primary efficacy outcome [total venous thromboembolism (VTE) and all-cause mortality] comparing rivaroxaban with enoxaparin for thromboprophylaxis after total hip or knee arthroplasty

rivaroxaban was administrated orally once daily with a dose of 10 mg in five RCTs, and orally twice daily with total daily dose of 10 mg in the other three dose-ranging RCTs. The trials included in our meta-analysis used the enoxaparin dose and regimen approved for use in Europe (six RCTs; 40 mg once daily, first dose received 12 h or the evening before surgery and medication resumed 6–8 h after wound closure) or in the USA (two RCTs: 30 mg twice daily, first dose received on the morning after surgery or 12–24 h after wound closure).

Efficacy outcomes

Data on primary outcome and secondary outcomes were provided in all eight relevant RCTs. Compared to enoxaparin, thromboprophylaxis with rivaroxaban was associated with significantly fewer total VTE and all-cause mortality (9,244 patients, RR 0.56, 95% CI 0.39–0.80), but a similar mortality (9,622 patients, RR 0.58, 95% CI 0.24–1.37).

Our meta-analysis of the primary outcome and secondary outcomes reveals the superiority of rivaroxaban over enoxaparin for thromboprophylaxis after total hip or knee arthroplasty.

In terms of the total hip arthroplasty subgroup, there were significantly fewer total VTE and all-cause mortality (5,491 patients, RR 0.49, 95% CI 0.25-0.98), deep-vein

In the total knee arthroplasty subgroup, there were significantly fewer total VTE and all-cause mortality (3,753 patients, RR 0.66, 95% CI 0.48-0.91) and

The separate analyses of the total hip and knee arthroplasty subgroups produced findings similar to those of the overall meta-analysis.

Safety outcomes

All eight RCTs provided the relevant safety outcomes.

Our analysis of total bleeding events also revealed that there were no significant differences in the incidence of bleeding events between the rivaroxaban groups and enoxaparin groups (13,384 patients, RR 1.10, 95% CI

Fig. 3 Meta-analyses of the incidence of the secondary efficacy outcome comparing rivaroxaban with enoxaparin for thromboprophylaxis after total hip or knee arthroplasty. **a** Major VTE, **b** deep-vein thrombosis, **c** symptomatic VTE

0.97–1.24; Fig. 4c).

The safety analysis revealed that the benefits of rivaroxaban for thromboprophylaxis were not obtained at the expense of a significant increased risk of bleeding, although numerically higher bleeding events did occur in the rivaroxaban groups.

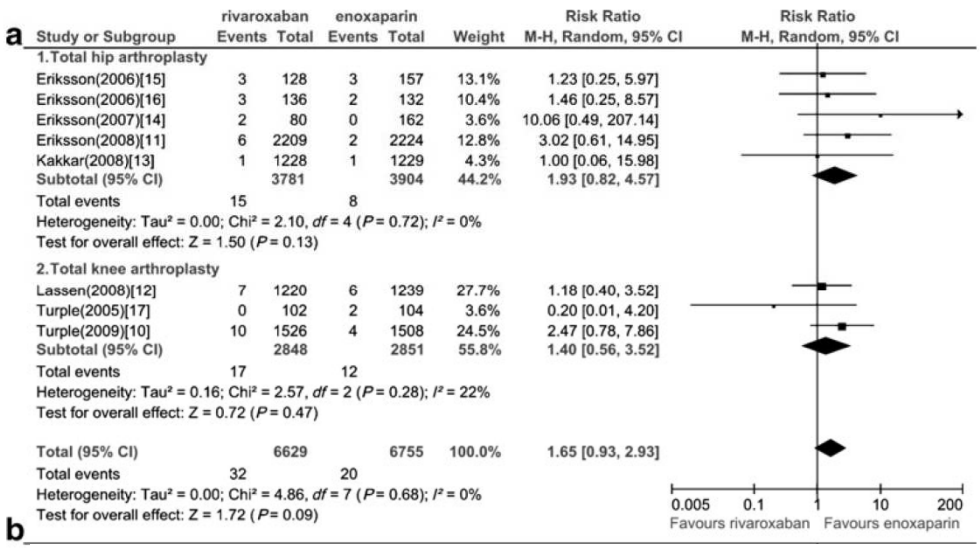

Fig. 4 Meta-analyses of incidence of bleeding events comparing rivaroxaban and enoxaparin for thromboprophylaxis after total hip or knee arthroplasty. **a** Major bleeding, **b** clinically relevant non-major bleeding, **c** total bleeding events

Sensitivity analysis

The sensitivity analysis limited to double-blind RCTs did not change the efficacy and safety findings for the review overall. Removal of each individual study or those studies of lower quality also did not significantly affect our primary outcome. The sensitivity analysis of the alternative inclusion of other rivaroxaban dosage groups in the dose-ranging studies again did not significantly change the overall efficacy and safety findings of the study. The results

Fig. 5 Meta-analyses of incidence of drug-related adverse events comparing rivaroxaban and enoxaparin for thromboprophylaxis after total hip or knee arthroplasty

of the analysis that only included those trials using 40 mg of enoxaparin once daily were similar to those of the overall meta-analysis in terms of efficacy and safety.

Discussion

The overall finding of our meta-analysis suggests that thromboprophylaxis with rivaroxaban (total daily dose of 10 mg) was superior to that with the recommended dose of enoxaparin (Figs. 2, 3).The safety outcome analysis revealed that the benefit of rivaroxaban for thromboprophylaxis was not associated with an increasing risk of both bleeding (Fig. 4) and drug-related adverse events (Fig. 5).

The conclusion of this study is based on a pooled analysis of both total hip and knee arthroplasty trials. To avoid the influence of clinical heterogeneity, we performed a subgroup meta-analysis on the total hip and knee arthroplasty trials, respectively. The subgroup analysis also demonstrated that rivaroxaban had superior effect and a similar incidence of bleeding for thromboprophylaxis, showing findings that were unchanged with those of the overall review.

In conclusion, despite the limitations of our meta-analysis, we suggest that rivaroxaban appears to be more effective than enoxaparin for thromboprophylaxis after hip and knee arthroplasty and that the benefits of rivaroxaban in VTE prevention were not gained at the expense of an increased risk of bleeding. Current evidence suggests that rivaroxaban, an effective direct factor Xa inhibitor which is given in a fixed, unmonitored oral dose, is an alternative to enoxaparin for preventing VTE after hip and knee arthroplasty. However, well-designed head-to-head RCTs focusing on the bleeding risk of rivaroxaban compared with enoxaparin are warranted.

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Conflict of interest The authors state that they have no conflict of interest.

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