Meta analysis

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

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Keywords: *embolism; prophylaxis; anticoagulants; apixaban; meta-analysis*

Background Enoxaparin is routinely used for prevention of venous thromboembolism (VTE) after total hip or knee arthroplasty. The purpose of this study was to compare the efficacy and safety of apixaban, a newly oral direct inhibitor of factor Xa versus enoxaparin.

Methods We performed a meta-analysis of relevant randomized-controlled trials (RCTs) identified in PubMed, Cochrane Library, Embase China Biological Medical Literature database, Countries Journal full-text database, VIP database, and WanFang database. The primary efficacy outcome for our meta-analysis was all VTE and all-cause mortality. The secondary efficacy outcomes included major VTE, non-fatal pulmonary embolism, and mortality. The primary safety outcome was bleeding events, categorized as major, clinically relevant non-major, or minor events.

Results Four RCTs, involving 14 065 patients, were included in our meta-analysis. Compared to enoxaparin, thromboprophylaxis with apixaban was associated with significantly fewer VTE and all-cause mortality (8346 patients, risk ratio (*RR*): 0.63, 95% *CI* 0.42–0.95) and similar incidence of bleeding events (major bleeding, 11 525 patients, *RR* 0.76, 95% *CI* 0.43–1.33; clinically relevant non-major bleeding, 11 525 patients, *RR* 0.83, 95% *CI* 0.69–1.01; and minor bleeding, 11 828 patients, *RR* 0.93, 95% *CI* 0.79–1.09). However, our meta-analysis revealed similar effects of apixaban with enoxaparin for thromboprophylaxis with regard to the secondary efficacy outcomes.

Conclusions Apixaban was more effective than recommended dose of enoxaparin and had a similar safety profile for thromboprophylaxis after hip and knee arthroplasty. But more evidence, especially well designed head-to-head RCTs, is needed to confirm the superior efficacy of apixaban.

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Several randomized controlled trials (RCTs) have been done to compare the efficacy and safety of apixaban with enoxaparin, which is the most widely used LMWH for thromboprophylaxis after total hip or knee arthroplasty.[10-13] Results from these RCTs have indicated that apixaban was an efficacious and promising agent for thromboprophylaxis after total hip or knee arthroplasty and has a better efficacy than enoxaparin. In the study reported here, our aim was to compare more conclusively the efficacy and safety of apixaban with enoxaparin for thromboprophylaxis by performing a meta-analysis of

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relevant RCTs.

METHODS

Data sources

The study was performed using a pre-specified search strategy and study eligibility criteria. We did an extensive search of PubMed (up to March 2012), the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2012), Embase (1980 to March 2012), China Biological Medical Literature database (1980 to March 2012), Countries Journal Full-text database (1980 to March 2012), VIP database (1980 to March 2012), and WanFang database (1980 to March 2012) to identify relevant RCTs for our meta-analysis. We restricted the search to RCTs. Search term combinations were "apixaban", "enoxaparin", "low molecular weight heparins", "total knee arthroplasty" and "total hip arthroplasty", and "thromboprophylaxis" and "venous thromboembolism". 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 (LI Xiu-min and SUN Shi-guang) independently searched the literatures and examined relevant RCTs for further assessment. Any study was included in our meta-analysis if it was a RCT; if it included patients of all ages undergoing total hip or knee arthroplasty; and if it compared the efficacy and safety of apixaban with enoxaparin for thromboprophylaxis. Trials with blinded and unblinded design were both included. Abstracts in scientific conferences were not included in the meta-analysis. 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 (LI Xiu-min and SUN Shi-guang) using the Jadad scoring system as follows:[14] One point is awarded for the presence of randomization, blinding, and data about 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 regarding 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 higher than 2 is considered as an RCT of adequately good quality.[15,16] Standard criteria (allocation concealment, blinding, intention-to-treat (ITT) analysis, and follow-up) were also used to appraise the study quality in addition to the Jadad scoring system.

Data extraction

Data were independently extracted by two investigators (LI Xiu-min and SUN Shi-guang) and checked by the other authors. The concordance rate between the two investigators was 95.3%. Data were extracted from each study with a predesigned review form. In case of any disagreement between the two reviewers, a third reviewer extracted the data and 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) during treatment, and follow-up were extracted.

Analyzed outcomes

The primary efficacy outcome of this meta-analysis was all VTE and all-cause mortality (the composite of adjudicated asymptomatic or symptomatic deep-vein thrombosis (DVT), non-fatal pulmonary embolism, or death from any cause during the intended treatment period).

The primary safety outcome of the meta-analysis was bleeding events, categorised as major, clinically relevant non-major bleeding, or minor bleeding events during the treatment period or until 2 days after the last dose of study medication was administered. The definition of major bleeding was adapted from the criteria for bleeding in non-surgical patients of the International Society of Thrombosis and Haemostasis.[17]

Data analysis and statistical methods

Statistical analyses were performed with Review Manager version 5.1.1 (Cochrane Collaboration, Oxford, UK). The heterogeneity of trial results was assessed by calculating a χ^2 test of heterogeneity and the I^2 measure of inconsistency. Publication bias was assessed by examining the funnel plot. A random-effects model was used by applying the DerSimonian-Laird method for pooling risk ratios (*RR*s) and 95% confidence intervals (*CI*s) throughout the meta-analysis, which accounts for both within-study and between-study variations.[18] A sensitivity analysis was performed by omitting one study in turn to investigate the influence of a single study on the overall meta-analysis estimate.[19]

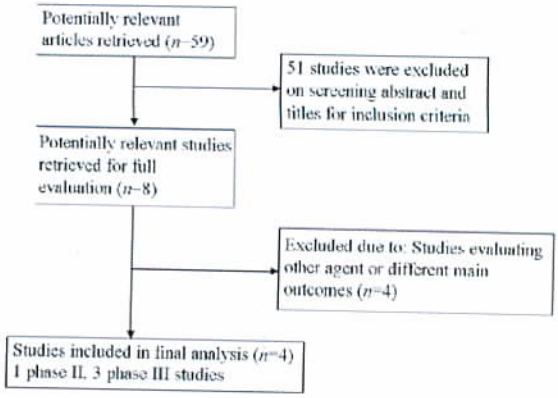

Figure 1. Flow diagram of the randomized controlled trials (RCTs) reviewed.

RESULTS

Study selection process

The flow diagram (Figure 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 eight full papers from 59 studies for detailed evaluation and ultimately identified four RCTs, including one phase II and three phase III studies, which fulfilled all of the criteria for inclusion in the meta-analysis.

Study characteristics

The main characteristics of the four 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 14 065 patients.

Efficacy outcomes

Data about primary outcome and secondary outcomes were provided in all four relevant RCTs. Compared to enoxaparin, thromboprophylaxis with apixaban associated witp[h significantly fewer primary outcomes (all VTE and all-cause mortality) occurred (8346 patients, *RR*: 0.63, 95% *CI* 0.42–0.95, Figure 2), presenting a superior effect of apixaban compared to enoxaparin for thromboprophylaxis after total hip or knee arthroplasty.

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

Studies	Type of studies	Included population	Drug tested		Number of enrolled patients	Jadad score
			Apixaban	Enoxaparin		
ADVANCE-3 (2010)[10]	Multicentre double-blind RCT	Adults who were scheduled to undergo elective total hip arthroplasty	Apixaban 2.5 mg, orally twice daily, started 12–24 hours after closure of the surgical wound	Enoxaparin 40 mg, subcutaneous injections once daily with the first dose was started 12 hours (within 3 hours) before surgery	5765	5
ADVANCE-2 (2010)[11]	Multicentre double-blind RCT	Adults who were scheduled to undergo elective total knee arthroplasty	Apixaban 2.5 mg, orally twice daily, started 12–24 hours after closure of the surgical wound	Enoxaparin 40 mg, subcutaneous injections once daily with the first dose was started 12 hours (within 3 hours) before surgery	3221	5
ADVANCE-1 (2009)[12]	Multicentre double-blind RCT	Adults who were scheduled to undergo elective total knee arthroplasty	Apixaban 2.5 mg, orally twice daily, started 12–24 hours after completion of the surgery	Enoxaparin 30 mg, subcutaneous injections twice daily, started 12–24 hours after completion of the surgery	3608	5
APROPOS (2007)[13]	Multicentre double-blind RCT	Adults (≥18 years old) who were scheduled to undergo elective total knee arthroplasty	Apixaban 2.5 mg, 5 mg or 10 mg orally twice daily, started 12–24 hours after completion of the surgery	Enoxaparin 30 mg, subcutaneous injections twice daily, started 12–24 hours after completion of the surgery	1471	5

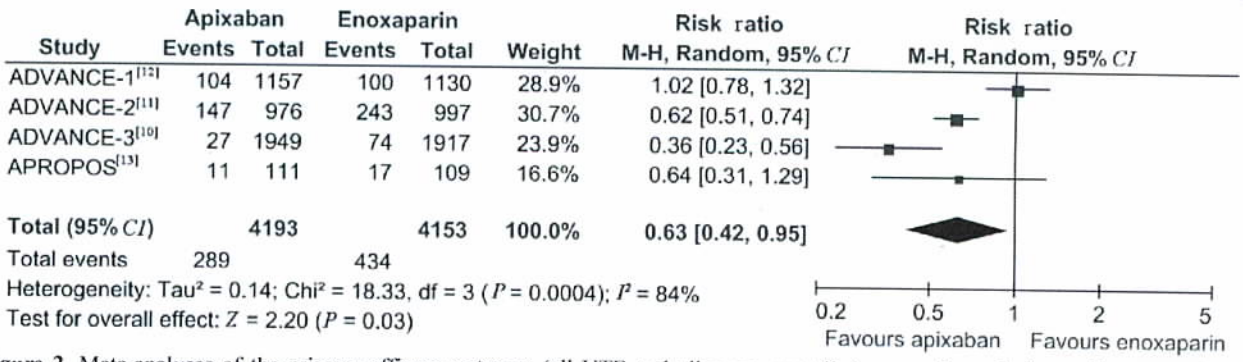

Figure 2. Meta-analyses of the primary efficacy outcome (all VTE and all-cause mortality) comparing apixaban with enoxaparin for thromboprophylaxis after total hip or knee arthroplasty.

Safety outcomes

All the four RCTs provided the relevant safety outcomes. Our meta-analysis indicated that low numbers of each kind of bleeding events occurred in the apixaban groups; however, no significant differences was found between the apixaban groups and enoxaparin groups (major bleeding, 11 525 patients, *RR* 0.76, 95% *CI* 0.43–1.33; clinically relevant non-major bleeding, 11 525 patients, *RR* 0.83, 95% *CI* 0.69–1.01; and minor bleeding, 11 828 patients, *RR* 0.93, 95% *CI* 0.79–1.09, Figure 4).

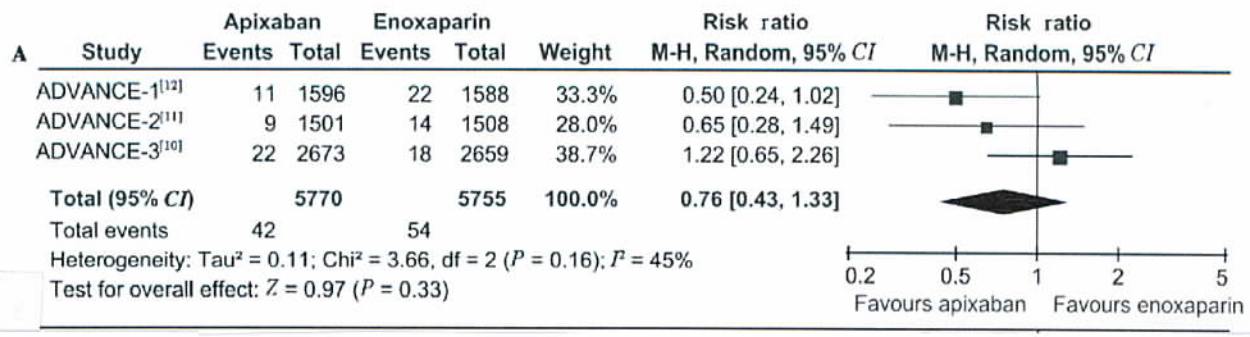

Figure 4. Meta-analyses of incidence of bleeding events (**A:** major bleeding; **B:** clinically relevant non-major bleeding; **C:** minor bleeding; **D:** total bleeding events) comparing apixaban and enoxaparin for thromboprophylaxis after total hip or knee arthroplasty.

DISCUSSION

The use of oral anticoagulants may lead to more convenient and safe antithrombotic therapies with increased patient compliance compared to LMWHs and vitamin K antagonists. These oral agents have the potential to act as treatment alternatives to LMWHs and vitamin K antagonists after major joint arthroplasty and in atrial fibrillation. The major oral anticoagulants in current use are the newly developed direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban, etc.).

risk of bleeding.

The result of our meta-analysis indicated better efficacy of apixaban compared to enoxaparin for thromboprophylaxis with regard to the primary efficacy outcome (all VTE and all-cause mortality). However, this finding should be interpreted with caution, given that the meta-analysis of all three secondary efficacy outcomes (major VTE, non-fatal pulmonary embolism, and mortality) revealed that apixaban did not show substantial advantage compared to enoxaparin, suggesting that the superior efficacy of apixaban need to be confirmed by more evidence, especially well designed head-to-head RCTs.

One widely recognized impediment to effective thromboprophylaxis in patients undergoing total hip or knee arthroplasty is concern about the risk of bleeding.[4] In this regard, our meta-analysis, based on currently available data, is reassuring in that even though it was found to be superior to enoxaparin for thromboprophylaxis, apixaban was not associated with significant increases in bleeding events, conversely with a numerically lower incidence of each kind of bleeding events and significantly lower incidence of total bleeding events. In terms of the risk of bleeding, our meta-analysis suggested that apixaban was associated with a favorable benefit compared to enoxaparin, but we also stress that apixaban should be contraindicated in patients susceptible to hemorrhage.

Both recent evidence-based guidelines issued by the American College of Chest Physicians (ACCP) and the UK National Institute for Health and Clinical Excellence (NICE) recommend extended prophylaxis against VTE for patients undergoing total hip or knee arthroplasty.[1,21] The patients are generally required to continue receiving thromboprophylaxis treatment after hospital discharge, but subcutaneous administrations of LMWHs and vitamin K antagonists often result in fewer patients receiving the duration of prophylaxis recommended by the guidelines.[1,21] Apixaban not only can be administered in a fixed, unmonitored dose as enoxaparin, but also can be given orally which may lead to more convenient and safe antithrombotic therapies with increased compliance. Therefore, in addition to potential superior efficacy and safety profile, the fixed, unmonitored, oral dose also makes apixaban an attractive alternative to enoxaparin for thromboprophylaxis after total hip or knee arthroplasty.

To our knowledge, the present study is the first systematic review with a meta-analysis comparing apixaban with enoxaparin for thromboprophylaxis after total hip or knee arthroplasty. The main strength of our meta-analysis is that it is focused on high-quality RCTs with large number of patients (n=14 065). The efficacy and safety outcomes of our meta-analysis were defined similarly in both our meta-analysis and the individual included trials. In the included treatment arms, the same administration route and doses of apixaban (orally 2.5 mg twice daily) was used to compare with the standard enoxaparin dose. In all of the included trials, the presence of DVT was confirmed with ultrasonography or venography, and suspected pulmonary embolism was confirmed with ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography. The safety outcomes, bleeding events categorized according to severity, were also adapted from the same criteria. The similar treatment schedule and evaluation criteria of the included trials provided greater statistical confidence for our meta-analysis.

This meta-analysis is not without limitations. First, the meta-analysis is based on a relatively small number of RCTs and we acknowledge that using a limited number of studies raises the possibility of a second-order sampling error.[22] However, meta-analyses often include small numbers of studies; Higgins et al[22] evaluated 39 Cochrane reviews and found that 67% of them included ≤5 studies and 20% included ≤10 studies. A lower threshold for the number of studies to be included in a meta-analysis has not yet been established.[22,23] Second, despite analysis efficacy outcomes by pooling results from all the available properly randomized trials with large number of patients, our meta-analysis lacked statistical power to provide precise estimates of frequency and treatment effect for clinically important outcomes such as death from VTE. However, strategies that are effective for the total VTE, especially those proximally located, are likely also to be effective in the prevention of fatal VTE. Third, there was some heterogeneity between the RCTs included in our meta-analysis, such as different prophylactic duration and enoxaparin dose. Two RCTs included in our meta-analysis used the enoxaparin 40 mg once daily, while two RCTs used 30 mg twice daily. However, differences among trials are inevitable since each individual trial comprises different populations and uses different treatment protocols, and there is always some heterogeneity, even within individual trials.[24,25] Heterogeneity did not preclude pooling of their results because individual patients are directly compared only with other patients within the same trial, and not across the trials. The validity of our approach was also supported by sensitive analysis, which gained the similar efficacy and safety findings with the overall analysis. Fourth, another consideration that should be made was that four RCTs excluded patients with active bleeding, and all of the trials did not included adolescent and children patients. So the finding of this meta-analysis should be interpreted with caution on patients with active bleeding, adolescents, and children. Finally, all of the four included RCTs were supported by the branding pharmaceutical company of apixaban, which might generate bias in the assessment of outcomes. Nevertheless, the sensitivity analysis performed in our meta-analysis obtained findings similar to those of the primary analysis. Due to the above limitations, the superior efficacy of apixaban yet needs to be confirmed by more well designed head-to-head RCTs.

In conclusion, despite the limitations of our meta-analysis, we conclude that apixaban appears to be more effective than enoxaparin for thromboprophylaxis after hip and knee arthroplasty and that the benefits of apixaban in VTE prevention were not gained at the expense of an increased risk of bleeding. Current evidence suggested that apixaban, 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.

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