

Apixaban versus enoxaparin in patients with total knee arthroplasty

A meta-analysis of randomised trials

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Summary

It was the objective of this study to systematically compare the effects of apixaban versus enoxaparin in patients following total knee arthroplasty (TKA). A systematic search of Medline, EMBASE, Cochrane Central Register of Controlled Trials was conducted. Eligible studies were prospective, randomised control trials (RCT) of apixaban therapy, comparing with enoxaparin, in patients who have a high risk of venous thromboembolism (VTE) after TKA. Three RCTs involving 7,337 individuals were identified, of whom 4,057 were treated with apixaban 2.5 mg once daily, and 3280 were subcutaneous enoxaparin (40 mg once-daily or 30 mg twice-daily). Meta-analysis demonstrated the odds ratio (OR) for the composite of major VTE (proximal deep-vein thrombosis and pulmonary embolism) for apixaban versus enoxaparin was 0.47 (95% confidence interval [CI]: 0.27 to 0.82, 0.6% vs. 1.2%) and 2.09 (95%CI:

0.99 to 4.45, 0.6% vs. 0.3%), respectively. All-cause mortality occurred in 0.2% of the apixaban group versus 0.09% of the enoxaparin group (OR=1.74; 95%CI, 0.51 to 5.95). With respect to safety outcomes, apixaban was associated with a lower major bleeding rate than enoxaparin (OR=0.55, 95%CI: 0.32 to 0.96). No significant differences were detected between two strategies in other endpoints of safety profile analysed: clinically relevant non-major bleeding, raised hepatic transaminase enzyme or bilirubin concentrations and arterial thromboembolic events. In conclusion, apixaban is non-inferior to subcutaneous enoxaparin when used for the same duration, with considerable advantage regarding safety profile of major bleeding after TKA.

Keywords

Apixaban, enoxaparin, total knee arthroplasty, meta-analysis

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Introduction

Despite available anticoagulant prophylaxis after surgery, patients who undergo total knee arthroplasty (TKA) have a high incidence of venous thromboembolism (VTE). VTE (including deep-vein thrombosis [DVT] and pulmonary embolism [PE]), which is a major, potentially fatal complication after TKA, develops soon after surgery in 30 to 40% of those who undergo TKA (1, 2). The use of low-molecular-weight heparin (LMWH), vitamin K antagonists, and mechanical methods to prevent venous thromboembolism after TKA is current standard practice. However, practical limitations of these methods may limit optimal patient care, since they require subcutaneous injection (heparins) or careful dose adjustment (vitamin K antagonists) or tend to be cumbersome (mechanical devices).

Apixaban, which has high oral bioavailability in rats, dogs, and humans confirmed by preliminary studies (3, 4), is a highly potent and reversible, direct inhibitor of factor Xa, with greater than

30,000-fold selectivity over other coagulation proteases (5). Furthermore, the competent pharmacokinetic characteristics of the compound are found to have multiple pathways of elimination, including renal and faecal excretion, minimal potential for drug-drug interactions and the formation of reactive metabolites (3).

Three multicentre, randomised, double-blind trials have compared the efficacy and safety of apixaban, starting postoperatively, with subcutaneous in patients undergoing TKA. However, individual trials have not been large enough to explore outcomes reliably within subgroups. Therefore, meta-analysis that allows for the pooling and quantification of results from different studies is required to overcome the limitation. To date, no meta-analysis has been conducted that evaluates the available evidence for a comparison between apixaban and enoxaparin. For these reasons, we performed a meta-analysis of randomised trials, with sufficient sample size and power gained through combining the results of several studies in a rigorous scientific overview, to investigate the efficacy and safety outcomes of oral apixaban, relative to the sub-

cutaneous enoxaparin, for the prevention of VTE in patients who had undergone TKA.

Methods

Data sources

A comprehensive search was performed to identify randomised controlled trials (RCTs) in Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the citation database Web of science in any language between 1966 and July 2010, using the search terms apixaban, enoxaparin, total knee arthroplasty, and randomised controlled trials, as well as combinations of these terms. An independent search using Web of Science was done to ensure that all relevant clinical trials were included in the meta-analysis. In addition, bibliographies of retrieved articles were manually searched for other relevant studies.

Study selection

The goal of this study was to determine whether apixaban was associated with a lower incidence of VTE and no inferiority of safety profile in relation to enoxaparin. Therefore, inclusion criteria were a) prospective, randomised controlled trials either open-label or blinded; b) adults aged at least 18 years who were scheduled for elective TKA for one or both knees, including revision; c) assignment of participants to oral apixaban treatment or subcutaneous enoxaparin group; and d) available data including efficacy and safety outcomes, and sample size for analysis.

Quality assessment

Two reviewers evaluated each study both independently and in duplicate using a critical review checklist of the Dutch Cochrane Centre (6). The following methodological features most relevant to the control of bias were assessed: adequate sequence generation, allocation concealment, blinding, selective outcome reporting and other sources of bias. Each criteria was categorised as 'yes', 'no', or 'unclear', and the summary assessments of the risk of bias for each important outcome within and across studies was categorized as 'low risk of bias', 'unclear risk of bias' and 'high risk of bias'.

Data extraction

Two independent investigators abstracted the data in a traditionalised format independently and in duplicate. The following baseline characteristics were extracted: first author, publication year,

country, study duration, follow-up, participant characteristics (patient number, mean age, and sex ratio), treatment duration, duration of prophylaxis and intervention. Both of the investigators for each participating trial provided the major VTE, all-cause mortality, major and clinically relevant non-major bleeding events, liver enzyme elevation and acute coronary events, and the composites of these endpoints during treatment and/or follow-up time. Outcomes were collected for patients in each treatment group from randomisation to hospital discharge. All of the collected data were verified by each of the participating investigators. Discrepancies in data extraction were to be resolved by consensus, referring back to the original article, and by contacting the study authors if necessary.

Outcome measures

The primary efficacy endpoint, a composite of asymptomatic or symptomatic DVT, PE and all-cause mortality during treatment, is commonly used in trials of VTE prophylaxis, for it is very sensitive to the treatment effect and allows trials of reasonable size to be conducted. Nevertheless, a reasonably high rate of asymptomatic distal DVT that may not be so relevant to routine clinical practice should be taken into account. Therefore, the primary efficacy endpoint for our pooled analysis was considered as the composite of major VTE (asymptomatic or symptomatic proximal DVT and objectively confirmed PE), which was recommended by European regulatory authorities for a therapeutic claim of VTE prevention (7). For the primary endpoint of major VTE, patients must have had an evaluable bilateral venography for proximal DVT, or verified symptomatic PE with the use of ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography. Secondary efficacy outcome was all-cause mortality. For deaths, autopsy was performed whenever possible for any cause of death.

The primary safety endpoint of the analysis was the frequency of major bleeding events occurring during the treatment period or within two days after the last dose of study medication. Secondary safety outcomes included rates of clinically relevant non-major bleeding events, raised hepatic transaminase enzyme or bilirubin concentrations (≥ 3 times the upper limit of the normal reference range (ULN) for serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT], ≥ 2 times the ULN for serum bilirubin) and arterial thromboembolic events (defined as confirmed myocardial infarction, acute ischaemic stroke, or other systemic thromboembolism) occurring during the treatment period and follow-up. Major and clinically relevant non-major bleeding events were defined according to the trial reported previously (8).

Data synthesis

Version 9.2 of the Stata[®] program (Stata Corporation, College Station, TX, USA) was used for statistical analysis. Data were ana-

lysed by a modified intention-to-treat population, which consisted of all randomised patients who received at least one dose of study treatment for the safety population and comprised all patients who were randomised, received at least one dose of study treatment, underwent surgery, and had evaluable centrally adjudicated data for VTE or who died during treatment for the efficacy endpoints.

To standardise reporting of our results, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from raw data of every trial. For the meta-analysis, we initially used the fixed-effects model (9), based on inverse variance weights for combined results from the individual trials. The Cochran's X^2 and the I^2 statistic were first calculated to assess the heterogeneity among the proportions of the included trials. If the p-value was less than 0.1 and where I^2 was greater than 50%, the assumption of homogeneity was deemed invalid, and the following techniques were employed to explore the heterogeneity: (i) subgroup analysis; (ii) sensitivity analysis performed by omitting one study in each turn and investigated the influence of a single study on the overall meta-analysis estimate when necessary; (iii) if the heterogeneity still existed, randomised-effects models as described by DerSimonian and Laird were applied to incorporate between-study heterogeneity in addition to sampling variation for the calculation of summary OR estimates and corresponding 95% CIs. Otherwise, the pooled event rate data for each treatment group were presented alongside the common OR results obtained from the pooled analysis in fixed-effects model. The Egger regression test, Begg adjusted rank correlation test, and visual inspection of a funnel plot were performed to assess publication bias (10, 11). A two-tailed p-value of less than 0.05 was considered statistically significant.

This work was performed in accordance with the Quality of Reporting of Meta-analyses (QUOROM) guidelines for meta-analysis of randomized clinical trials (12).

Results

Study characteristics

The search strategy yielded 42 references: Medline (N = 5), Embase (N = 34), and CENTRAL (N = 3). A total of 11 potentially eligible studies were identified by literature search. We excluded seven studies that were just review articles. One study was excluded because it was based on acute coronary syndromes. Therefore, three randomised clinical trials (8, 13, 14) were finally determined to be eligible for inclusion criteria and they were invited to collaborate for the purpose of analysis. The flow chart of the literature search of this meta-analysis is shown in ► Figure 1. Two trials tested the efficacy and safety of apixaban versus enoxaparin in patients undergoing TKA (apixaban was given as a divided, twice-daily [b.i.d.] dose of 2.5 mg), and one trial had multiple arms (to test the three total daily doses of 5, 10 and 20 mg apixaban, given either as a once-daily [q.d.] or a divided, b.i.d. dose to patients following elective TKA). All the studies included in the meta-analysis were reasonably well conducted and had balanced populations. Of the 7,337 participants, 4,057 were randomised to apixaban therapy, and 3,280 were randomised to enoxaparin therapy. Patient enrolment ranged between 152 and 1,599, mean age of patients ranged from 65.6 to 67.2 years, and the duration of hospital stay ranged from 6–38.0 days. Details of the included studies are summarised in the ► Table 1.

In a phase II study (14), the dose identified as appropriate for patients undergoing major joint surgery was 2.5 mg of apixaban administered twice daily. Therefore, for each trial the difference in the proportion of patients with an event (efficacy or safety) was collaborated and compared between 2.5 mg apixaban dose group and enoxaparin as an OR as this was the most clinically meaning-

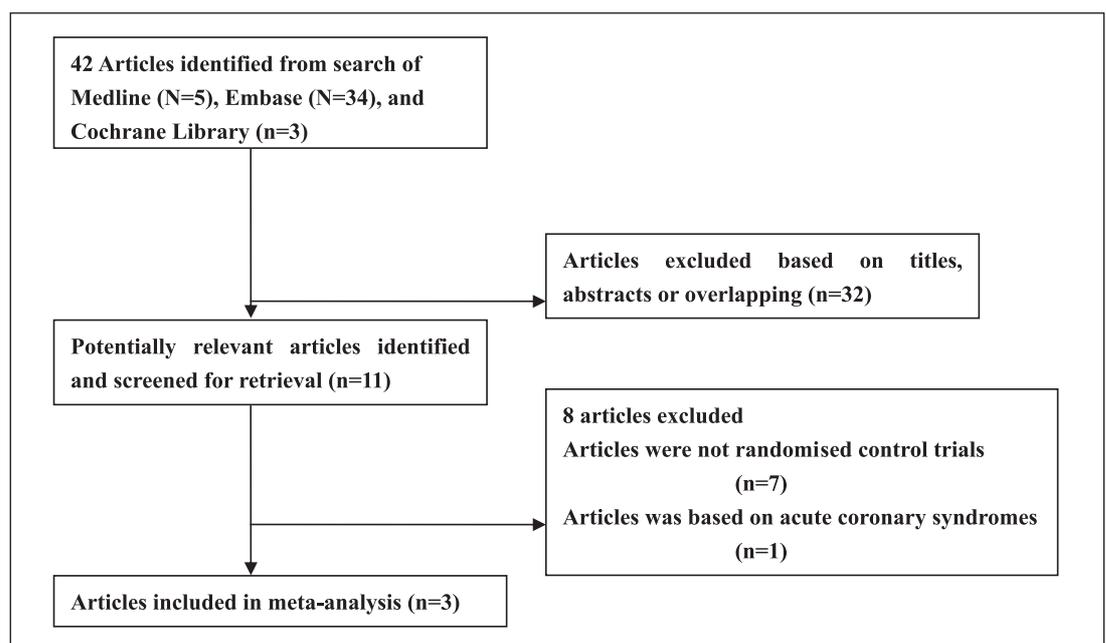


Figure 1: Flow-chart of study selection.

Table 1: The baseline characteristics of the trials.

First author year	Country	Study design	Treatment duration	Duration of prophylaxis (days)	Follow-up (days)	Treatment groups	Patients			Sur-gery	Intervention
							N	Age (years)	Male/ female		
Lassen 2010[13]	Denmark	Multicentre RCT	June 2007 to Nov. 2008	12.0	60	Apixaban	1528	65.6	439/1089	TKA	Apixaban 2.5 mg, b.i.d
				12.0		Enoxaparin	1529	65.9	402/1127		Enoxaparin 40 mg, q.d*
Lassen 2009[8]	Denmark	Multicentre RCT	NA	10.0–14.0	60	Apixaban	1599	65.9	602/997	TKA	Apixaban 2.5 mg, b.i.d
				10.0–14.0		Enoxaparin	1596	65.7	610/986		Enoxaparin 30 mg, b.i.d‡
Lassen 2007[14]	Denmark	Multicentre RCT	NA	10.0–14.0	NA	Apixaban	153	67.6	49/104	TKA	Apixaban 2.5 mg, b.i.d
				10.0–14.0		Apixaban	157	66.9	55/102		Apixaban 5 mg, q.d
				10.0–14.0		Apixaban	157	66.4	54/103		Apixaban 5 mg, b.i.d
				10.0–14.0		Apixaban	156	67.2	64/92		Apixaban 10 mg, q.d
				10.0–14.0		Apixaban	154	66.4	59/95		Apixaban 10 mg, b.i.d
				10.0–14.0		Apixaban	156	65.8	45/101		Apixaban 20 mg, q.d
				10.0–14.0		Enoxaparin	152	66.5	62/94		Enoxaparin 30 mg, b.i.d‡
				10.0–14.0							

TKA, total knee arthroplasty; q.d., once daily; b.i.d., twice daily; NA, not available; RCT, randomised control trial. *start before surgery and resume after operation; ‡starting 12–24 h after surgery.

ful measure. Lassen et al. (13) compared apixaban with enoxaparin 40 mg q.d initiated pre-operatively, while Lassen et al. (8) and Lassen et al. (14) compared with enoxaparin 30 mg bid initiated post-operatively. Meta-analyses were therefore performed for Lassen et al. (8) and Lassen et al. (14) (representing the comparison of apixaban with the 30 mg enoxaparin b.i.d. post-operatively dose specifically), as well as analyses including all three trials (which synthesised all available evidence for apixaban 2.5 mg vs. enoxaparin for VTE prophylaxis following TKA).

Quality assessment of the trials

Treatment assignments were the typical method of “randomisation” across trials in this meta-analysis. Randomised treatment allocation sequences were generated in all trials. It was clearly stated in the original papers that blinded fashion was conducted across trials and the outcome measurements were not likely to be influenced by lack of blinding. The numbers and reasons for withdrawal/dropout were detailed reported across trials. None had stopped early due to data-dependent process or other problems, so

free of other sources of bias were defined across trials. Thus, all the including studies (8, 13, 14) were determined as low risk of bias (plausible bias unlikely to seriously alter the results).

Efficacy

Proximal DVT

The event of proximal DVT was explored across the three trials, and the incidence of proximal DVT in the apixaban group was 19/3,251 (0.6%) and the enoxaparin group was 40/3,245 (1.2%). Pooled analysis of OR in fixed-effects model showed proximal DVT was significantly less prominent among participants receiving apixaban in relation to enoxaparin, and the results were robust, with no evidence of heterogeneity (OR=0.47, 95%CI: 0.27 to 0.82, $p=0.007$; p of heterogeneity= 0.327, $I^2=10.6\%$, ► Fig. 2).

PE

PE data required for meta-analysis was available from three studies. Two of them recorded a higher rate of PE, but one study

showed that there was a higher rate of PE in enoxaparin group. Pooled analysis of OR showed apixaban was not associated with a significant reduction in the risk of PE when compared with enoxaparin, and no heterogeneity was detected across trials (OR=2.09, 95%CI: 0.99 to 4.45, p=0.055; p of heterogeneity=0.184, I²=40.8%; ► Fig. 3).

All-cause mortality

Among patients who received apixaban, the incidences of all-cause mortality in these studies ranged between 0.13% and 0.65%, with the highest incidence observed in the trial of patients with the smallest largest population. The incidence of all-cause mortality in the enoxaparin group was only occurred in the trial with the largest population. Using a fixed-effects model, meta-analysis revealed that the summary incidence of all-cause mortality was not significantly higher in apixaban group and there was no heterogeneity

among the studies (OR=1.74; 95%CI, 0.51 to 5.95, p =0.378; p for heterogeneity= 0.595, I² = 0.0%).

Subgroup analysis

Whether enoxaparin timing and total daily dose are clinically important remains uncertain since head-to-head comparisons are scarce. Therefore, we performed an exploratory analysis stratified by the different regimens of enoxaparin administration. Synthesis of the two-trial data slightly altered the conclusions of the analyses including all three trials. There was no significant difference in the OR between apixaban and enoxaparin for the pooled proximal DVT analysis and no evidence of significant heterogeneity (OR=0.71, 95%CI: 0.31 to 1.95, p=0.402; p of heterogeneity=0.450, I²=0.0%; ► Fig. 2). The OR between apixaban and

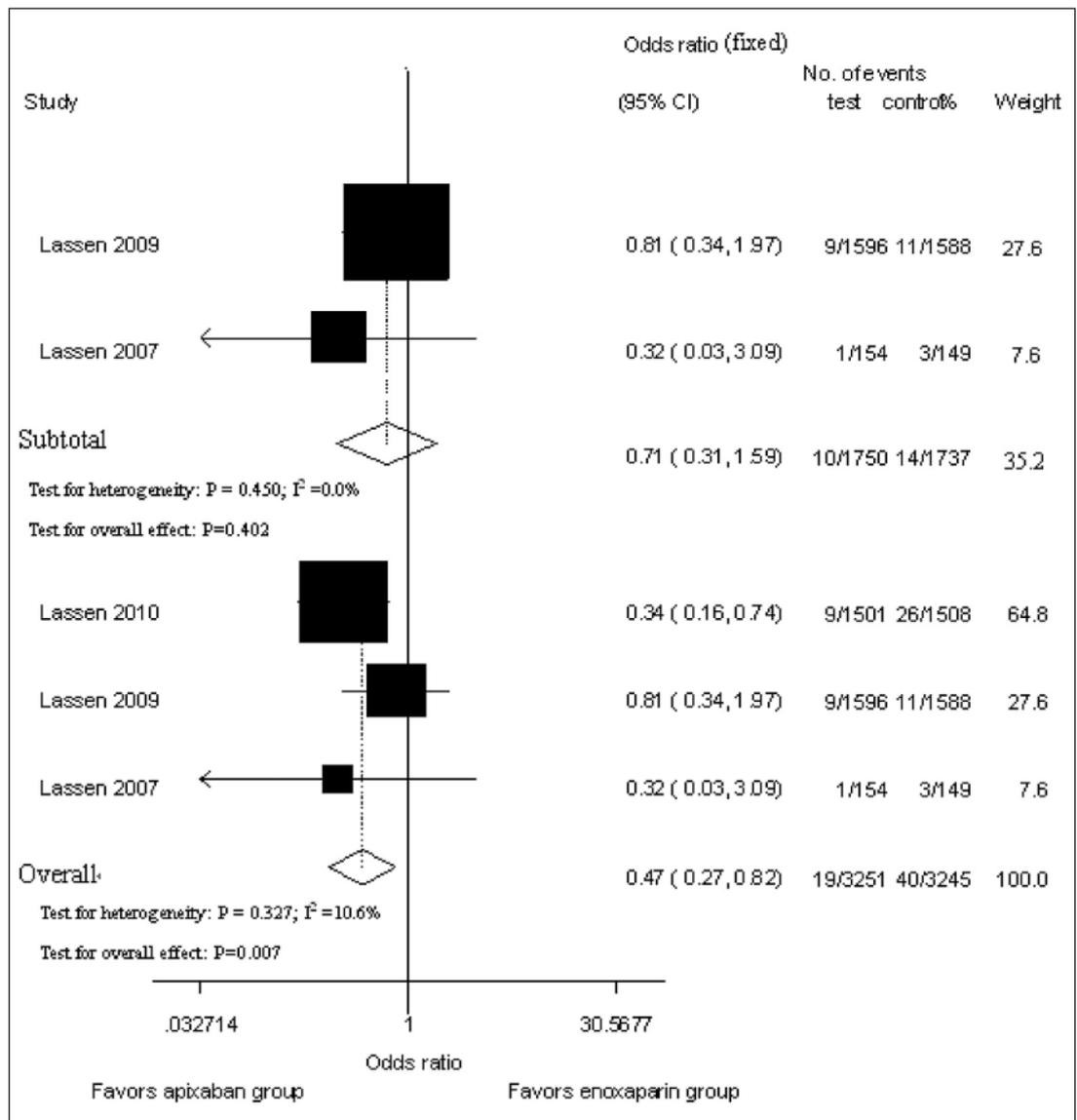


Figure 2: Fixed-effects model of odds ratio (95% confidence interval) of proximal deep-vein thrombosis associated with apixaban in relation to enoxaparin.

enoxaparin for each the pooled analyses of PE ranged from 0.78 to 3.84, indicative of a consistent treatment effect between two regimens, and substantial heterogeneity was detected between the trials. Thus, randomised-effects model was applied to yield wider CIs allowing for trial heterogeneity (OR=1.73, 95%CI: 0.78 to 3.84, $p=0.181$; p of heterogeneity=0.122, $I^2=58.2\%$). The result of all-cause mortality was robust and no heterogeneity was detected across trials according to subgroup analysis and consistent with the combined analysis (OR=1.27, 95%CI: 0.31 to 5.15, $p=0.736$; p of heterogeneity=0.555, $I^2=0.0\%$; ► Fig. 3)

Safety

Major bleeding

Bleeding can delay recovery and can predispose to infections which endanger the prosthesis. The overall incidence of major bleeding was 0.85%, with the incidence of major bleeding in the apixaban group was 20/3,097 (0.6%) and the enoxaparin group was 36/3,096 (1.2%) according to our meta-analysis of trials with available data in two trials (8, 13). Compared with controls, the OR of major bleeding associated with apixaban treatment was 0.55 (95%CI: 0.32 to 0.96, $p=0.034$), indicating participants receiving apixaban had significant reduction in the composite of major bleeding in relation to control, and there was no heterogeneity among the studies (p of heterogeneity= 0.641, $I^2=0.0\%$).

Clinically relevant non-major bleeding

Three trials (8, 13, 14) reported clinically relevant non-major bleeding including 85 of 3,280 (2.6%) patients in the apixaban group and 111 of 3,277 (3.4%) patients in the enoxaparin group. The pooled analysis did not show significant difference between two groups, with no heterogeneity across studies (OR=0.76, 95%CI: 0.57 to 1.01, $p=0.058$; p of heterogeneity= 0.910, $I^2=0.0\%$).

Liver function

Few patients in either treatment group had raised hepatic transaminase enzyme or bilirubin concentrations during treatment and follow-up period. Meta-analysis of two trials (8, 13) showed the frequency serum AST and ALT did not differ between two groups according to the pooled estimate for OR, with significant heterogeneity across these trials (OR=0.95, 95%CI 0.62 to 1.47, $p=0.826$; p of heterogeneity= 0.047, $I^2=74.6\%$). Owing to heterogeneity can not be eliminated by sensitivity analysis, randomised-effect model was performed with an outcome of OR equal to 0.95 and 95% CI of 0.40–2.28 and p -value equal to 0.912.

The pooled data of serum bilirubin of two trials (8, 13) denoted statistically significant heterogeneity between the two groups (p of heterogeneity=0.024, $I^2=80.4\%$), and a randomised-effects model was applied (OR=0.76, 95%CI: 0.10 to 5.59, $p=0.788$; p of heterogeneity= 0.024, $I^2=80.4\%$).

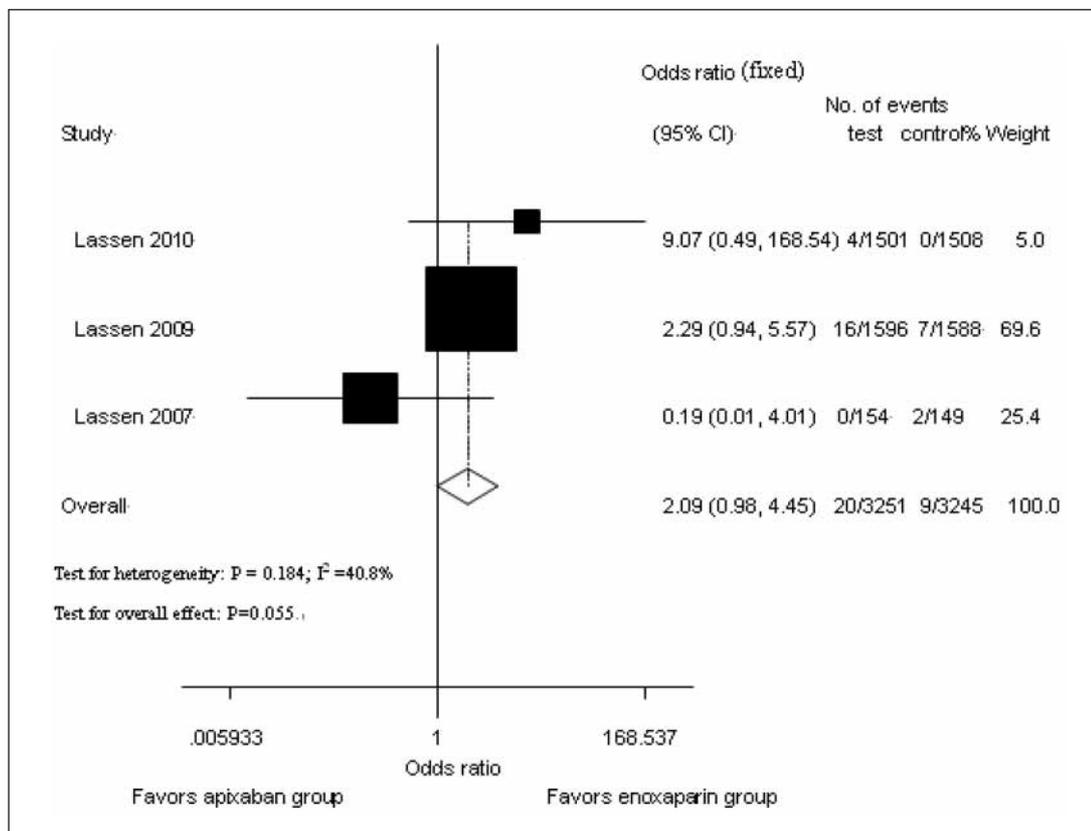


Figure 3: Fixed-effects model of odds ratio (95% confidence interval) of pulmonary embolism associated with apixaban in relation to enoxaparin.

Table 2: Efficacy outcomes of meta-analysis comparing apixaban versus enoxaparin in patients with TKA.

Efficacy outcomes	Trials	Apixaban	Enoxaparin	Heterogeneity		OR (95%CI)	P-value
		n/N (%)	n/N (%)	P-value	I ²		
Proximal DVT	3	19/3251 (0.6%)	40/3245 (1.2%)	0.327	0.106	0.47 (0.27–0.82)	0.007
PE	3	20/3251 (0.6%)	9/3245 (0.3%)	0.184	0.408	2.09 (0.98–4.45)	0.055
All-cause mortality	3	6/3251 (0.2%)	3/3245 (0.09%)	0.595	0	1.74 (0.51–5.95)	0.378

DVT, deep-vein thrombosis; n, number; PE, pulmonary embolism; TKA, total knee arthroplasty.

Table 3: Safety outcomes of meta-analysis comparing apixaban versus enoxaparin in patients with TKA.

Safety outcomes	Trials	Apixaban	Enoxaparin	Heterogeneity		OR (95%CI)	P-value
		n/N (%)	n/N (%)	P-value	I ²		
Major bleeding	2	20/3097 (0.6%)	36/3096 (1.2%)	0.641	0	0.55 (0.32–0.96)	0.034
Clinically relevant non-major bleeding	3	85/3251 (2.6%)	111/3245 (3.4%)	0.910	0	0.76 (0.57–1.01)	0.058
Serum AST+ALT $\geq 3 \times$ ULN	2	41/3097 (1.3%)	43/3096 (1.4%)	0.047	0.746	0.95 (0.40–2.28)	0.912
Serum bilirubin $\geq 2 \times$ ULN	2	17/3097 (0.5%)	16/3096 (0.5%)	0.024	0.804	0.76 (0.10–5.59)	0.788
Myocardial infarction	3	4/3251 (0.1%)	5/3245 (0.2%)	0.289	0.195	0.81 (0.23–2.82)	0.738
Stroke	3	3/3251 (0.09%)	5/3245 (0.2%)	0.289	0.193	1.28 (0.32–5.16)	0.733

TKA, total knee arthroplasty; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Arterial thromboembolic events

Three trials (8, 13, 14) reported myocardial infarction including four of 3,251 patients (0.1%) in the apixaban group and five of 3,245 patients (0.2%) in the control. The pooled analysis did not show significant difference between two groups, with no heterogeneity across studies (OR=0.81, 95%CI: 0.23 to 2.82, $p=0.738$; p of heterogeneity= 0.289, $I^2=19.5\%$).

There was not significant difference in the pooled OR of stroke of three trials (8, 13, 14) (OR=1.28, 95%CI 0.32 to 5.16, $p=0.733$), and no heterogeneity across trials was detected by the X^2 test, with p -value 0.289 ($I^2=19.3\%$).

Subgroup analysis

There were no significant differences between the treatment groups with respect to clinically relevant non-major bleeding (Fixed, OR=0.76, 95%CI: 0.50 to 1.15, $p=0.196$; p of heterogeneity=0.665, $I^2=0.0\%$), myocardial infarction (random, OR=0.91, 95%CI: 0.05 to 16.63, $p=0.949$; p of heterogeneity=0.118, $I^2=59.0\%$) and stroke (fixed, OR=0.65, 95%CI: 0.11 to 3.94, $p=0.643$; p of heterogeneity=0.232, $I^2=29.9\%$) according to subgroup analysis, which was consistent with the combined analyses.

► Tables 2 and 3 list the efficacy and safety outcomes of particular interest, without any adjustment in the median duration of therapy.

Publication bias

Inspection of funnel plots and statistical tests for publication bias did not show an obvious effect of publication bias (Egger's test, $p=0.198$; Begg's test, $p=1.000$).

Discussion

Patients undergoing TKA are at high risk of VTE if they do not receive anticoagulants. For this reason, current treatment guidelines for patients following TKA recommend the routine administration of a prophylactic anticoagulant for at least 10 days after the operation (2). The contribution of apixaban, a potent and reversible inhibitor of factor Xa, to the prevention of VTE is difficult to assess as individual RCTs are not powered to detect a significant relationship. Our study pooled data from three major RCTs to overcome this limitation and perform a meta-analysis comparing apixaban 2.5 mg b.i.d. with enoxaparin for VTE prophylaxis following TKA suitable for the purposes of prophylactic technology appraisal. Results of this meta-analysis demonstrated that apixaban was more effective than enoxaparin in decreasing the risk of proximal DVT, but no statistically significant differences were detected in any other endpoint of efficacy, including PE and all-cause mortality. In our analysis of efficacy, tests for heterogeneity found no convincing evidence of a difference in treatment effect among trials. However, we should consider that there are inherent differences in trial design; therefore we performed subgroup analysis according to different regimens of enoxaparin administered. Enoxaparin administered at 30 mg b.i.d. starting after surgery has never been

prospectively compared with enoxaparin 40 mg administered before surgery and resumed an average of 19 hours after operation. The indirect comparison that was made by the two trials (8, 13) invited speculation that twice daily 30 mg enoxaparin in Lassen et al. (8) could be more effective, but have a higher tendency to bleeding, whereas 40 mg per day enoxaparin in Lassen et al. (13) could be less effective, but was safer than the b.i.d. dosage. The evidence from subgroup analysis suggested that the 30 mg b.i.d. regimen of enoxaparin provided non-inferior efficacy to the 2.5 mg b.i.d. regimen of apixaban, with respect to proximal DVT, PE and all-cause mortality. Our stratified analysis suggested a moderate degree of heterogeneity between trials related to PE (where the regimen of apixaban and enoxaparin was the same in the two trials); importantly, the heterogeneity would be expected as a result of chance, which was not surprising given the certain differences in target populations. When the trials comparing apixaban 2.5 mg with enoxaparin 30 mg b.i.d. were meta-analysed, no significant differences were detected in any of the efficacy endpoints. Pooled analysis of all trials comparing apixaban 2.5 mg b.i.d. with enoxaparin supports the conclusions of the individual trials (Lassen et al. [8]), and strengthens the evidence that apixaban is superior to enoxaparin 40 mg q.d. when used for the same duration. In view of the results of our analysis, we tentatively conclude that apixaban is non-inferior to enoxaparin 40 mg q.d. when used for the same duration, and more high-quality RCTs with this particular dose of apixaban and enoxaparin are needed to confirm these findings.

With regard to safety profile, our analysis indicated that the safety outcomes associated with both apixaban therapy and enoxaparin therapy were comparable, except for major bleeding. Although the frequency of major bleeding events was low, with 0.6% in the apixaban group and 1.2% in the enoxaparin group, there was significantly less prominent major bleeding among participants receiving apixaban therapy in relation to control according to our meta-analysis. Due to unavailable data from Lassen et al. (14), subgroup analysis could not be applied to explore the impact of differences in the enoxaparin dosing regimen and timing of initiation of study treatment. Notably, patients with enoxaparin dose appeared to be

associated with higher major bleeding risk in relation to apixaban, suggesting that apixaban might be useful in these patients to reduce incidences of major bleeding when compared with each enoxaparin dose. The result of the meta-analysis of clinically relevant non-major bleeding comparing apixaban with enoxaparin was consistent with those of the individual trials; no statistically significant differences were detected in combined or subgroup analysis, with no evidence of statistical heterogeneity between trials.

Effects of apixaban on liver function were of special interest in our study. The risk of hepatic transaminase enzyme and bilirubin concentrations elevation during treatment period with apixaban was consistently low (0.1% to 2.0% of patients in each of the two trials had serum AST and ALT elevations $\geq 3x$ ULN, and serum bilirubin elevations $\geq 2x$ ULN) and similar to that observed with enoxaparin. The majority of these events were initially detected on the same day of study therapy. These observations from over 7,300 patients who received apixaban or enoxaparin were followed for at least two months and suggested that as for apixaban and enoxaparin, raised transaminase enzyme or bilirubin concentrations following TKA were benign and might be related to the surgical procedure or associated anaesthesia. These results suggested a greater level of heterogeneity than between trials, where p-values for heterogeneity were > 0.70 in the analyses, and it might be contribute to the inconsistent study design that comparing apixaban with different enoxaparin regimens.

The frequency of arterial thromboembolic events during treatment period and follow-up occurred in three patients (0.09%) who received apixaban and in five patients (0.2%) who received enoxaparin. The low incidences of reported adverse events were similar in the two groups, and were supportive of a lack of rebound activation of coagulation following treatment without continuation.

A feature of many large-scale studies is that patients are lost to analyses if the evaluation methodology is suboptimum or not done. As in our analysis, 552 (36%) of 1,528 and 532 (35%) of 1,529 apixaban and enoxaparin patients could not be assessed for the primary efficacy outcome in Lassen et al. (13), compared with 442 (28%) of 1,599 and 466 (29%) of 1,596 apixaban and enoxaparin patients in Lassen et al. (8). Probable rates of patients who could not be assessed for efficacy were unlikely to yield unbalanced because their baseline demographics were similar between the two study groups, as were non-assessable reasons and randomisation was stratified by study centre to avoid imbalance. Furthermore, blinded fashion was conducted to reduce ascertainment bias to a minimum. Crucially, data of meta-analysis were analysed by a modified intention-to-treat population, which comprised all randomised patients who received at least one dose of study treatment and plausible bias unlikely to seriously alter the main study findings.

Our findings are based on a pooled analysis of more than 7,300 patients who underwent TKA and had prophylactic anticoagulation for VTE. To our knowledge, these results represent the first reported pooled comparison of VTE prevention following apixaban or enoxaparin. We performed a comprehensive search of available literature and identified several high-quality randomised

What is known about this topic?

- The use of low-molecular-weight heparin, vitamin K antagonists, and mechanical methods to prevent venous thromboembolism after total knee arthroplasty (TKA) is current standard practice.
- Three multicentre, randomised, double-blind trials have compared the efficacy and safety of the new factor Xa inhibitor apixaban in patients undergoing TKA. However, individual trials have not been large enough to explore outcomes reliably within subgroups.

What does this paper add?

- We systematically compared the effects of apixaban versus enoxaparin in patients following TKA.
- Apixaban is non-inferior to subcutaneous enoxaparin when used for the same duration, with considerable advantage regarding safety profile of major bleeding after TKA.

clinical studies of patients suitable. The definition of outcome measures was clearly defined and this would have resulted in precise outcomes. Results of this meta-analysis were also supported by the absence of significant heterogeneity for primary efficacy and safety event rates across the individual studies included in our analysis.

However, we do acknowledge that there are several limitations of the present study needed to be considered. First, although the three trials included were designed similar to compare 2.5 mg apixaban with enoxaparin, there were differences in the dosing regimens of the comparator. Nevertheless, these differences may lack any impact in clinical practice, for actual dose regimens of anticoagulant therapy used differ from regulatory recommendations. Second, heterogeneity detected from safety endpoints of liver function limited comparability between studies and affects the validity of these results. The number of eligible studies is not enough to perform sensitivity analysis and only a randomised-effects model was applied to overcome this shortcoming. The validity of these results needs higher quality RCTs for confirmation. Third, when we performed an exploratory analysis stratified by different regimens of enoxaparin, we were subjected by the small sample of a trial included (14), which were not powered to detect a significant relationship.

In conclusion, the meta-analysis of the trials comparing apixaban with enoxaparin demonstrates that apixaban is non-inferior to enoxaparin when used for the same duration, with considerable advantage regarding safety profile of major bleeding. In clinical practice, apixaban can be considered an alternative to conventional thromboprophylaxis regimens in patients undergoing elective TKA, taking into account each patient's clinical circumstances and economic advantages. Larger prospective RCTs with particular regimen are warranted in order to draw firm conclusions about clinical benefit and risks.

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