ARTHRoplasty

Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement

POOLED ANALYSIS OF MAJOR VENOUS THROMBOEMBOLISM AND BLEEDING IN 8464 PATIENTS FROM THE ADVANCE-2 AND ADVANCE-3 TRIALS

In order to compare the effect of oral apixaban (a factor Xa inhibitor) with subcutaneous enoxaparin on major venous thromboembolism and major and non-major clinically relevant bleeding after total knee and hip replacement, we conducted a pooled analysis of two previously reported double-blind randomised studies involving 8464 patients. One group received apixaban 2.5 mg twice daily (plus placebo injection) starting 12 to 24 hours after operation, and the other received enoxaparin subcutaneously once daily (and placebo tablets) starting 12 hours (± 3) pre-operatively. Each regimen was continued for 12 days (± 2) after knee and 35 days (± 3) after hip arthroplasty. All outcomes were centrally adjudicated.

Major venous thromboembolism occurred in 23 of 3394 (0.7%) evaluable apixaban patients and in 51 of 3394 (1.5%) evaluable enoxaparin patients (risk difference, apixaban minus enoxaparin, -0.8% (95% confidence interval (CI) -1.2 to -0.3); two-sided p = 0.001 for superiority). Major bleeding occurred in 31 of 4174 (0.7%) apixaban patients and 32 of 4167 (0.8%) enoxaparin patients (risk difference -0.02% (95% CI -0.4 to 0.4)). Combined major and clinically relevant non-major bleeding occurred in 182 (4.4%) apixaban patients and 206 (4.9%) enoxaparin patients (risk difference -0.6% (95% CI -1.5 to 0.3)).

Apixaban 2.5 mg twice daily is more effective than enoxaparin 40 mg once daily without increased bleeding.

Ideally, a new anticoagulant regimen for thromboprophylaxis in arthroplasty surgery of the lower limb would achieve improved efficacy with a lower or similar bleeding risk, or similar efficacy with less bleeding, than in existing practice. Often, however, new anticoagulant regimens have achieved better antithrombotic efficacy at the expense of an increased risk of bleeding.1-6 Low-molecular-weight heparins are recommended for operative venous thromboembolism,17,18 A pre-specified aim of the apixaban development programme was to provide more precise estimates of the incidence of major venous thromboembolism by pooling data from the two comparisons of apixaban with the same enoxaparin regimen (ADVANCE-2 and -3). Major venous thromboembolism was pre-defined as the composite of proximal deep-vein thrombosis (DVT), non-fatal pulmonary embolism and death related to venous thromboembolism.18

The primary efficacy outcome measure for these and other phase-3 clinical trials of new anticoagulant regimens after hip or knee arthroplasty was the occurrence of any post-operative venous thromboembolism, including isolated calf-vein thrombosis.1-6,10-16 Many surgeons and some regulatory agencies do not consider isolated calf-vein thrombosis as a relevant outcome for evaluating the benefit of thromboprophylaxis.17,18 A pre-specified aim of the apixaban development programme was to provide more precise estimates of the incidence of major venous thromboembolism by pooling data from the two comparisons of apixaban with the same enoxaparin regimen (ADVANCE-2 and -3). Major venous thromboembolism was pre-defined as the composite of proximal deep-vein thrombosis (DVT), non-fatal pulmonary embolism and death related to venous thromboembolism.18

The pooled analysis also enabled more precise estimates of bleeding rates to be made using...
pre-specified definitions of severity.\textsuperscript{10,11} We now report this pooled analysis, focusing on major venous thromboembolism as the outcome measure of efficacy and on clinically relevant bleeding, including bleeding at the surgical site, to provide a clinically useful risk–benefit assessment for practicing orthopaedic surgeons.

**Patients and Methods**

A total of 8464 patients were randomised in the ADVANCE-2 (knee arthroplasty) and ADVANCE-3 (hip arthroplasty) clinical trials. Patients were eligible if they were scheduled to undergo elective primary or revision knee or hip replacement. Major exclusion criteria were active bleeding, a contraindication to anticoagulant prophylaxis, or the need for ongoing anticoagulant or antiplatelet treatment.\textsuperscript{10,11} Additional criteria were uncontrolled hypertension, active hepatobiliary disease, impaired renal function (creatinine clearance < 30 ml/min), thrombocytopenia (platelets < 100 000/mm\textsuperscript{3}), anaemia (haemoglobin < 10 g/dl), heparin allergy or a history of heparin-induced thrombocytopenia, allergy to radiological contrast dye, or other disorders preventing bilateral venography, or a planned indwelling intrathecal or epidural catheter that could not be removed at least five hours before the first post-operative dose of the study drug. Prisoners, patients compulsorily detained for psychiatric or medical reasons, and patients who had received any investigational drug within the previous 30 days were also excluded. The complete inclusion and exclusion criteria are listed in the online appendices to the individual publications.\textsuperscript{10,11}

**Study designs and drug regimens.** The ADVANCE-2 and -3 studies were conducted as randomised double-blind dummy clinical trials (Clinicaltrials.gov numbers NCT00452530 and NCT00423319). They were designed and supervised by the ADVANCE Steering Committee, which approved the statistical analysis plan before database lock, had full access to data and analyses, wrote the manuscript, and vouched for its accuracy and completeness. Study protocols were approved by the ethics committee or institutional review board of each study centre. An independent Data Safety Monitoring Board regularly reviewed efficacy and safety data for each trial.

Potentially eligible patients were identified at screening visits up to 14 to 18 days before surgery; they signed written informed consent before enrolment, and were then randomly assigned, using an interactive telephone system, to receive apixaban 2.5 mg orally twice daily plus placebo injections or enoxaparin 40 mg subcutaneously once daily plus placebo tablets. The randomisation schedules were generated centrally using Statistical Analysis System software (SAS; SAS Institute, Cary, North Carolina), and were stratified by study site, and, in the ADVANCE-2 trial, by unilateral or bilateral surgery.

The same enoxaparin and apixaban regimens were evaluated in both trials. The subcutaneous enoxaparin or placebo was started 12 hours (± 3) before operation and resumed afterwards according to the investigator’s standard of care. The first dose of oral apixaban or placebo was given 12 to 24 hours after closing the wound, typically on the morning after surgery, with no restrictions on diet or timing of meals. Intrathecal or epidural anaesthetic devices were to be removed at least five hours before the first post-operative dose of oral drug. The drugs were continued for 10 to 14 days in the ADVANCE-2 trial\textsuperscript{10} and for 32 to 38 days in the ADVANCE-3 trial,\textsuperscript{11} consistent with the practice guidelines of the American College of Chest Physicians (ACCP).\textsuperscript{7}

Both studies used the same protocol to ascertain outcomes. Bilateral venography was scheduled at the end of the intended treatment period to assess the presence or absence of asymptomatic DVT.\textsuperscript{10,11,19} In hospital, all patients were assessed daily for symptomatic DVT and pulmonary embolism, bleeding and wound complications. Clinically suspected DVT was confirmed or excluded with ultrasonography or venography, and suspected pulmonary embolism with CT, ventilation–perfusion lung scanning or pulmonary angiography. All thromboembolic events detected were managed according to local practice. In case of death, autopsy was performed whenever possible. All patients underwent follow-up evaluation at 30 days (± 5) and 60 days (± 5) after the last dose of study medication, which included a clinical history, with assessment of symptoms and signs of venous thromboembolism, bleeding or adverse events, and laboratory tests including liver enzymes; objective testing for venous thromboembolism was performed at the discretion of the physician.

All venograms and episodes of suspected venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia or death were adjudicated by an independent central committee blinded to the treatment assigned. The determination of whether bleeding involved the surgical site was based on the reports provided by investigators.

**Outcome measures.** The pre-specified outcome measure of efficacy for this pooled analysis was major venous thromboembolism, defined as the composite of adjudicated symptomatic or asymptomatic proximal DVT (popliteal, femoral or iliac vein), non-fatal pulmonary embolism and death from venous thromboembolism.\textsuperscript{10,11,18}

The pre-specified outcome measures for bleeding were major bleeding, clinically relevant non-major bleeding, the composite of major and clinically relevant non-major bleeding, and any bleeding.\textsuperscript{10,11} Major bleeding was defined as acute clinically overt bleeding accompanied by one or more of the following: decrease in blood haemoglobin level of 2 g/dl or more over a 24 hour period; transfusion of two or more units of packed red blood cells; critical site bleeding (including intracranial, intraspinal, intra-ocular, peri-cardial or retroperitoneal); bleeding into the operated joint requiring reoperation or intervention; intramuscular bleeding with compartment syndrome; or fatal bleeding.\textsuperscript{20} Clinically relevant non-major bleeding included acute clinically overt episodes such as wound...
haematoma, bruising/ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that did not meet the criteria for major bleeding (descriptions are provided in the online appendices of the trial publications).10,11

Additional safety measures included myocardial infarction or stroke, and elevated hepatic transaminase enzyme and/or bilirubin levels, occurring during treatment or follow-up.

**Statistical analysis.** The ADVANCE-2 and -3 studies were each designed to test the hypothesis that apixaban would not be inferior to enoxaparin.10,11 The statistical analysis plans for both studies pre-specified that tests for superiority

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**Fig. 1**

Study flow (* patients who received at least one dose of study medication; † or underwent venography outside of the intended treatment period; DVT, deep-vein thrombosis; VTE, venous thromboembolism).
would be carried out if apixaban met the specified criteria for non-inferiority.\textsuperscript{10,11} Furthermore, it was pre-specified that pooled analyses would be performed using the data from the ADVANCE-2 and -3 studies, which used the same comparator regimen of enoxaparin 40 mg once daily\textsuperscript{10,12} and that results from the ADVANCE-1 trial would not be included in the pooled analysis because that study used a different comparator regimen of enoxaparin 30 mg twice daily.\textsuperscript{12}

Regarding efficacy, it was pre-specified that the pooled analysis would focus on the outcome of major venous thromboembolism. The population for this analysis included all the randomised patients who had a venogram adjudicated as having evaluable proximal veins, irrespective of whether the distal segments were adequately visualised, and all patients who had symptomatic proximal DVT or pulmonary embolism (Fig. 1). The time period for analysis was the intended treatment period for each trial, or within two days after the last dose of study medication, whichever was longer.

The population for analysis of bleeding and additional safety outcomes included all the randomised patients who had received at least one dose of the study drug (Fig. 1). Two distinct time periods for these analyses were pre-specified. The first was the period of treatment, which included all events occurring between the pre-operative dose and two days after the last dose of the drug, including any events that occurred before the first dose of oral drug. The second period for analysis included only the events occurring after the first post-operative dose of the study drug.

The pooled analysis included stratification for the type of joint replacement (hip or knee) and for unilateral or bilateral DVT, for joint replacement (hip or knee) and for unilateral or bilateral DVT.
Results

The demographic and clinical characteristics of patients in the apixaban and enoxaparin treatment groups are shown in Table I for each study and after pooling. A diagram of patient flow through the pooled analysis is shown in Figure 1.

Efficacy outcomes. The efficacy results are shown in Table II. Similar proportions of patients in the two treatment groups were evaluable for the outcome of major venous thromboembolism in each study (78% and 81%)\(^{10,11}\) and after pooling (80%) (Table II).

Major venous thromboembolism during the treatment period was observed in 23 of 3394 patients (0.7%) in the apixaban group and in 51 of 3394 patients (1.5%) in the enoxaparin group (risk difference (apixaban minus enoxaparin): -0.8% (95% CI -1.2 to -0.3); (one-sided p < 0.0001 for non-inferiority and two-sided p = 0.001 for superiority).

The test for heterogeneity of treatment effect between the ADVANCE-2 and -3 studies was not statistically significant (p = 0.66).

During the 60-day follow-up period symptomatic venous thromboembolism occurred in five patients in the apixaban group (0.1%) and eight patients in the enoxaparin group (0.2%) (p = 0.40).

Bleeding outcomes. The results are shown in Table III. Major bleeding occurred in 31 of 4174 patients (0.7%) in the apixaban group and 32 of 4167 patients (0.8%) in the enoxaparin group (risk difference (apixaban minus enoxaparin): -0.02 (95% CI -0.4 to 0.4)).

The incidences of bleeding at the surgical site are also shown in Table III for the categories of major bleeding, clin-
Table IV. Deaths during the treatment and follow-up periods* (PE, pulmonary embolism; VTE, venous thromboembolism)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of surgery</th>
<th>Treatment group</th>
<th>Adjudicated cause</th>
<th>On study medication</th>
<th>Day of event (relative to first dose of study drug)</th>
<th>Adjudicator comments</th>
<th>Autopsy – investigator comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Knee</td>
<td>Apixaban</td>
<td>Fatal PE</td>
<td>Yes</td>
<td>4</td>
<td>Acute abdominal</td>
<td>Autopsy performed. Thromboembolism of the pulmonary artery</td>
</tr>
<tr>
<td>2</td>
<td>Hip</td>
<td>Apixaban</td>
<td>Not VTE or bleeding</td>
<td>Yes</td>
<td>7</td>
<td>Cannot exclude fatal PE, sudden death</td>
<td>No autopsy performed. Abdominal compartment syndrome that led to multi-system organ failure</td>
</tr>
<tr>
<td>3</td>
<td>Hip</td>
<td>Apixaban</td>
<td>Fatal PE</td>
<td>Yes</td>
<td>9</td>
<td>Query infection and hepatitis, aspiration pneumonia, and multi-organ failure²</td>
<td>No autopsy performed. Cardio-respiratory failure</td>
</tr>
<tr>
<td>4</td>
<td>Knee</td>
<td>Apixaban</td>
<td>Not VTE or bleeding</td>
<td>Yes</td>
<td>13</td>
<td>Post-operative sepsis</td>
<td>No autopsy performed. Pulmonary and circulatory failure. Post-laparotomy. Colon tumour</td>
</tr>
<tr>
<td>5</td>
<td>Hip</td>
<td>Apixaban</td>
<td>Not VTE or bleeding</td>
<td>No</td>
<td>18</td>
<td>Cannot exclude fatal PE</td>
<td>No autopsy performed. Probable PE/myocardial infarction</td>
</tr>
<tr>
<td>6</td>
<td>Knee</td>
<td>Apixaban</td>
<td>Fatal PE</td>
<td>No</td>
<td>45</td>
<td>Bowel perforated and sepsis</td>
<td>Autopsy performed. Perforated bowel with secondary myocarditis</td>
</tr>
<tr>
<td>7</td>
<td>Hip</td>
<td>Apixaban</td>
<td>Not VTE or bleeding</td>
<td>Yes</td>
<td>47</td>
<td>Metastatic cancer colon</td>
<td>No autopsy performed. Metastatic colon cancer</td>
</tr>
<tr>
<td>8</td>
<td>Hip</td>
<td>Enoxaparin</td>
<td>Not VTE or bleeding</td>
<td>Yes</td>
<td>85</td>
<td>Metastatic cancer colon</td>
<td>Autopsy performed. Acute cardio-respiratory failure as a consequence of fat embolism of the terminal branches of the pulmonary arteries</td>
</tr>
<tr>
<td>9</td>
<td>Hip</td>
<td>Enoxaparin</td>
<td>Fatal bleeding²</td>
<td>No</td>
<td>1</td>
<td></td>
<td>Autopsy performed. Retroperitoneal bleed</td>
</tr>
<tr>
<td>10</td>
<td>Knee</td>
<td>Enoxaparin</td>
<td>Fatal PE</td>
<td>No</td>
<td>40</td>
<td></td>
<td>No autopsy performed. Cerebrovascular accident</td>
</tr>
<tr>
<td>11</td>
<td>Hip</td>
<td>Enoxaparin</td>
<td>Not VTE or bleeding</td>
<td>No</td>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* There were two additional deaths reported, but not included in any of the trial analyses. One occurred after the end of the follow-up period (day 159) in a patient randomised to apixaban and was adjudicated as not associated with VTE or bleeding. Another occurred in a patient who failed screening and was not randomised to either treatment group. This death was not adjudicated.
† On study medication when the serious adverse event associated with death occurred.
‡ This patient had study medication stopped on day 6 because of fever, jaundice and raised transaminase and bilirubin levels. Independent hepatologists masked to study treatment could not reach a diagnosis owing to lack of autopsy or a confirmed infectious organism, and a contribution of the study drug remains possible.
§ This patient died with retroperitoneal bleeding 40 days after surgery while taking a vitamin K antagonist for deep-vein thrombosis.

Critically relevant non-major bleeding and the composite. Major bleeding at the surgical site requiring reoperation or intervention occurred in two of the 4174 patients (0.05%) in the apixaban group and in one of the 4167 patients (0.02%) in the enoxaparin group. Table III also shows the incidences of bleeding at the surgical site with onset reported after the first dose of oral drug for each category of bleeding severity.

Additional safety outcomes. During the combined treatment and follow-up period, myocardial infarction or stroke occurred in 13 patients (0.3%) in the apixaban group and in ten patients in the enoxaparin group (risk difference (apixaban minus enoxaparin): 0.1% (95% CI -0.2 to 0.3). None of the strokes was haemorrhagic.

Deaths. A total of 11 patients died during the treatment or follow-up periods of these studies. The difference in the number of deaths between the treatment groups was not statistically significant (p = 0.23). The timings and causes of deaths are shown in Table IV.

Discussion
Our results indicate that apixaban 2.5 mg twice daily is more effective than 40 mg enoxaparin per day for preventing major venous thromboembolism after knee or hip arthroplasty, without increasing bleeding. The use of apixaban rather than the 40 mg enoxaparin regimen has been calculated to prevent one episode of major venous thromboembolism for every 125 patients treated.

Our analysis focused on major venous thromboembolism, which includes proximal DVT (asymptomatic or symptomatic) and pulmonary embolism (fatal or non-fatal). Major venous thromboembolism is considered by some regulatory agencies and by many surgeons to be a better measure of the clinical benefit of thromboprophylaxis because it does not include isolated asymptomatic calf-vein thrombosis. The improved efficacy of the apixaban regimen in preventing major venous thromboembolism was driven by its efficacy in preventing proximal DVT, most of which was asymptomatic (Table II). Asymptomatic proximal DVT is the source of most fatal pulmonary emboli. Most patients who die from pulmonary embolism do so abruptly, without cardiorespiratory warning symptoms or those of leg-vein thrombosis. The need for thromboprophylaxis is predicated on the fact that clinical surveillance alone, to detect and treat patients with symptomatic thromboembolism, is not effective in preventing fatal pulmonary embolism. Reducing the incidence of asymptomatic proximal-vein thrombosis, the main source of fatal embolic events, is therefore an important aim and benefit of any of thromboprophylactic regimen.
The overall mortality rate in the pooled analysis was low (0.13%, 11 of 8,464 patients), reflecting the excellent prognosis for these elective surgical patients who received effective thromboprophylaxis. Pulmonary embolism was the cause of death in only three of the 11 patients who died (Table IV). We used a conservative approach and attributed the cause of death to pulmonary embolism in all cases where another cause could not be established. The three deaths from pulmonary embolism in the apixaban group probably represent a chance variation of rare events, as the apixaban regimen reduced the incidence of proximal DVT, the precursor of fatal embolic events, by two-thirds (Table II), while at the same time the observed rates of symptomatic non-fatal pulmonary embolism were the same between the groups (Table II).

A potential limitation of thromboprophylaxis trials occurs when not all of the patients have a venogram of diagnostic quality. In our pooled analysis 80% of patients in each treatment group were evaluable for the efficacy outcome of major venous thromboembolism (Table II). This rate was similarly high and consistent in the two individual studies

The demographic and clinical characteristics of the patients evaluable for efficacy were very similar between the two groups (Table I). The reasons why patients were not evaluable for major venous thromboembolism were also similar between the groups (Fig. 1). These data suggest that the results of our efficacy analysis are likely to be valid.

The observed rates of each of the bleeding outcomes were similar to or lower for apixaban than for enoxaparin (Table III). The CIs for between-groups differences indicate that apixaban was unlikely (p < 0.025) to be associated with an increase in bleeding in more than three or four per 1000 patients (Table III). Importantly, major bleeding at the surgical site was not increased. Bleeding at the surgical site that required reoperation or intervention was very uncommon (< 1 in 1000 patients in both groups). These results indicate that the apixaban regimen had a favourable balance of antithrombotic benefit to bleeding risk compared with enoxaparin 40 mg once daily.

An advantage of the apixaban regimen for surgeons and anaesthetists is that prophylaxis is started 12 to 24 hours after operation. Our analysis of bleeding counted all events from the time of the pre-operative dose of study medication, as enoxaparin was begun pre-operatively. However, a proportion of bleeding events in the apixaban group occurred before patients had received their first dose of apixaban; this applied to 17 of the 26 major bleeding events at the surgical site (Table III). Therefore, the absolute incidence of major bleeding at the surgical site that may be attributable to apixaban was nine of 4174 (0.2%).

There has been concern that cardiovascular events such as myocardial infarction or stroke may be associated with use of the new oral anticoagulants. In our pooled analysis, although the observed number of patients with myocardial infarction was slightly higher in the apixaban group, the absolute risk difference observed was low (about 1 per 1000) and not statistically significant (p = 0.20), as the CI for the risk difference included zero difference and was relatively wide. The opposite trend was observed for stroke, with slightly more strokes in the enoxaparin group. Conclusions about the potential for small differences in the incidences of these cardiovascular outcomes must wait for data from ongoing clinical trials in more than 23,500 patients.23–25

The potential effects of a new oral anticoagulant medication on the liver are of interest in view of the experience with ximelagatran.26 Our pooled analysis did not suggest hepatotoxicity with apixaban. The rates of elevated transaminase enzymes were low and similar between the treatment groups, especially after removing patients who had an immediate enzyme or bilirubin elevation associated with their peri-operative care, including anaesthesia, blood transfusion and other drugs.

In conclusion, apixaban 2.5 mg twice daily is more effective than enoxaparin 40 mg once daily in preventing major venous thromboembolism (p = 0.001), without increased bleeding. The clinical advantages of oral administration and initiation 12 to 24 hours post-operatively provide a convenient form of thromboprophylaxis for use both in and out of hospital.

Supplementary material

Two tables showing the data regarding i) stroke and myocardial infarction and ii) hepatic enzyme elevations during the treatment and follow-up periods are available with the electronic version of this article on our website www.jbjs.org.uk

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References


