# Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

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## Summary

**Background** Low-molecular-weight heparins such as enoxaparin are preferred for prevention of venous thromboembolism after major joint replacement. Apixaban, an orally active factor Xa inhibitor, might be as effective, have lower bleeding risk, and be easier to use than is enoxaparin. We assessed efficacy and safety of these drugs after elective total knee replacement.

**Methods** In ADVANCE-2, a multicentre, randomised, double-blind phase 3 study, patients undergoing elective unilateral or bilateral total knee replacement were randomly allocated through an interactive central telephone system to receive oral apixaban 2·5 mg twice daily (n=1528) or subcutaneous enoxaparin 40 mg once daily (1529). The randomisation schedule was generated by the Bristol-Myers Squibb randomisation centre and stratified by study site and by unilateral or bilateral surgery with a block size of four. Investigators, patients, statisticians, adjudicators, and steering committee were masked to allocation. Apixaban was started 12–24 h after wound closure and enoxaparin 12 h before surgery; both drugs were continued for 10–14 days, when bilateral ascending venography was scheduled. Primary outcome was the composite of asymptomatic and symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death during treatment. The statistical plan required non-inferiority of apixaban before testing for superiority; analysis was by intention to treat for non-inferiority testing. The study is registered at ClinicalTrials.gov, number NCT00452530.

**Findings** 1973 of 3057 patients allocated to treatment (1528 apixaban, 1529 enoxaparin) were eligible for primary efficacy analysis. The primary outcome was reported in 147 (15%) of 976 apixaban patients and 243 (24%) of 997 enoxaparin patients (relative risk 0·62 [95% CI 0·51–0·74]; p<0·0001; absolute risk reduction 9·3% [5·8–12·7]). Major or clinically relevant non-major bleeding occurred in 53 (4%) of 1501 patients receiving apixaban and 72 (5%) of 1508 treated with enoxaparin (p=0·09).

**Interpretation** Apixaban 2·5 mg twice daily, starting on the morning after total knee replacement, offers a convenient and more effective orally administered alternative to 40 mg per day enoxaparin, without increased bleeding.

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*Listed in webappendix

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## Introduction

ADVANCE-2 is the second phase 3 study of three trials of efficacy and safety of apixaban for prevention of venous thromboembolism after elective total knee or hip replacement. Apixaban, an orally active factor Xa inhibitor, has the advantages of fixed daily dosing and low potential for drug interactions.[1] Prophylactic methods that are effective in major joint surgery include low-molecular-weight heparins, fondaparinux, and warfarin. Mechanical methods are recommended mainly for patients at high risk of bleeding or in addition to anticoagulants.[2] Enoxaparin, which is the most widely used low-molecular-weight heparin, has two approved dosing regimens: 40 mg per day starting 12 h before operation, and 30 mg twice daily beginning 12–24 h after surgery.[2] Low-molecular-weight heparins and fondaparinux need daily or twice daily subcutaneous injection and raise concerns about bleeding; delayed action makes warfarin fairly ineffective as short-term prophylaxis, and mechanical methods are cumbersome.[2] These limitations encouraged a search for straightforward methods that keep both thromboembolism and bleeding to a minimum.

Investigators have assessed several novel orally active anticoagulants in major joint surgery. Postoperative rivaroxaban, a factor Xa inhibitor, was more effective than was either enoxaparin regimen with a similar or perhaps slightly raised bleeding risk.[3–6] Two doses of postoperative dabigatran, a thrombin inhibitor, were non-inferior to enoxaparin 40 mg per day, but less effective than was enoxaparin 30 mg twice daily, and bleeding risk varied with timing of first dose.[7–9] In ADVANCE-1,[10] investigators compared apixaban 2·5 mg twice daily, starting 12–24 h after knee replacement, with postoperative enoxaparin 30 mg twice daily; the venous thromboembolism rates of 9·0% with apixaban and 8·8% with enoxaparin were clinically similar, but did not meet statistical criteria for non-inferiority, and reduced bleeding was reported with apixaban.

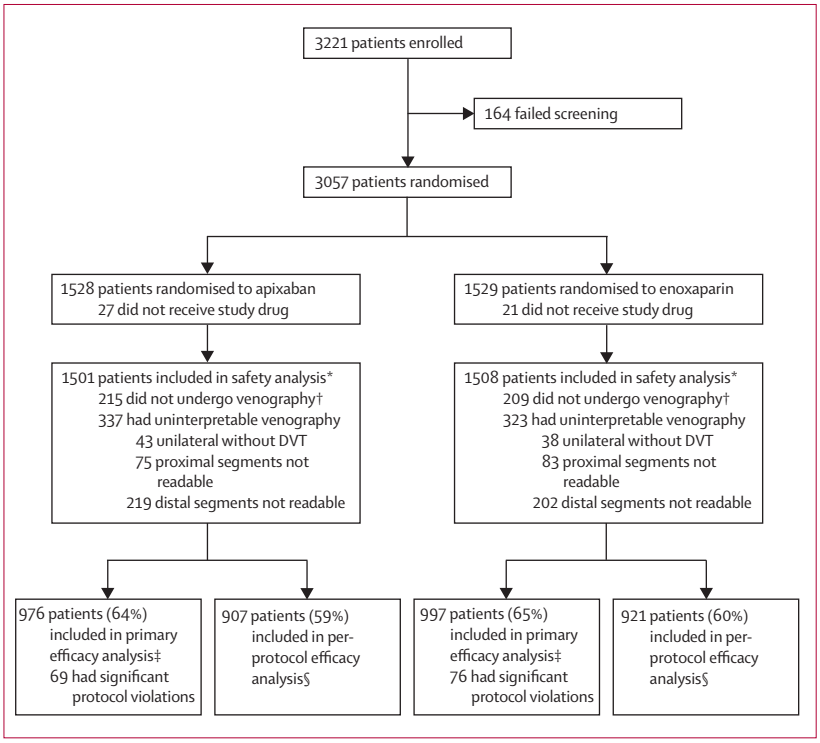


***Figure:*** **Trial profile**
DVT=deep vein thrombosis. *Patients who received at least one dose of study drug. †No venogram done or venogram done outside the intended treatment period. ‡Patients allocated to treatment who had interpretable venogram or adjudicated venous thromboembolism or who had died. §Excludes patients with significant protocol violations (webappendix).

See Online for webappendix

In ADVANCE-2, we aimed to compare efficacy and safety of oral apixaban, 2·5 mg twice daily, and of the widely used 40 mg per day enoxaparin regimen.

## Methods

### Patients and trial design

In ADVANCE-2, a multicentre, randomised, double-blind phase 3 study, patients were allocated to receive oral apixaban 2·5 mg twice daily, started 12–24 h after surgery, or 40 mg per day enoxaparin, started 12 h before operation. ADVANCE-2 was designed as a non-inferiority trial, because non-inferiority would be sufficient for an oral drug similar to apixaban, started after operation, to be clinically useful for surgical thromboprophylaxis.

Patients were eligible for the study if they were scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision. Patients were excluded if they had active bleeding or a contraindication to anticoagulant prophylaxis, or needed continuing anticoagulant or antiplatelet treatment. Additional exclusion criteria were uncontrolled hypertension, active hepatobiliary disease, impaired renal function, thrombocytopenia, anaemia, heparin allergy, allergy to radiographic contrast dye, or other disorders preventing bilateral venography.

### Randomisation and masking

Potentially eligible patients were identified during a screening period of up to 18 days before surgery. Eligible patients were enrolled after written informed consent was given and assigned through an interactive central telephone system to receive apixaban 2·5 mg orally twice daily and enoxaparin-matching placebo injections, or enoxaparin 40 mg subcutaneously once daily and apixaban-matching placebo tablets. The randomisation schedule was generated by the Bristol-Myers Squibb randomisation centre with SAS and was stratified by study site and by unilateral or bilateral surgery with a block size of four. Investigators, patients, statisticians, adjudicators, and the steering committee were masked to treatment allocation.

### Procedures

The first subcutaneous injection of study drug was given 12 h (within 3 h) before operation, and injections were resumed after surgery according to investigators' standard of care. The first dose of oral study drug was given 12–24 h after wound closure. There were no restrictions on diet or timing relative to food intake of oral drug. Typically, the first postoperative oral and subcutaneous doses of study drugs were given on the morning after surgery. The protocol required removal of intrathecal or epidural anaesthesia devices at least 5 h before first postoperative dose of oral study drug and of any pneumatic leg compression at wound closure. Twice daily oral drugs and once daily subcutaneous injections were continued for 10–14 days, when mandatory bilateral venography was scheduled.

In hospital, all patients had daily assessment for symptomatic deep vein thrombosis and pulmonary embolism, bleeding, and wound complications. Subclinical thrombosis at protocol-mandated venography was followed by continued prophylaxis or treatment, according to local practice. Objective testing was needed for clinically suspected venous thromboembolism. Patients had follow-up assessments 30 and 60 days after last dose of study drug. An independent central adjudication committee masked to treatment group adjudicated all venograms and episodes of suspected symptomatic venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia, or death.

The study was designed and supervised by the ADVANCE steering committee. In accordance with the Declaration of Helsinki, the protocol was approved by the ethics committee or institutional review board of every study centre, and investigators obtained written informed consent from patients before enrolment. An independent data and safety monitoring board regularly reviewed efficacy and safety data (members received a fee from the sponsor for professional services). The steering committee approved the statistical analysis plan before the database was locked.

| | Patients randomly allocated to treatment | | Primary efficacy population | |
|---|---|---|---|---|
| | Apixaban (n=1528) | Enoxaparin (n=1529) | Apixaban (n=976) | Enoxaparin (n=997) |
| Women | 1089 (71%) | 1127 (74%) | 687 (70%) | 730 (73%) |
| Age (years) | 67 (59–73; 65·6) | 67 (60–73; 65·9) | 66 (59–72; 65·1) | 67 (60–73; 66·0) |
| Weight (kg) | 78 (68·0–89·0; 78·7) | 78 (68·0–88·0; 78·3) | 78 (69·0–90·0; 79·2) | 78 (69·0–89·0; 78·5) |
| BMI (kg/m$^2$) | 29·1 (25·8–32·4; 29·3) | 29·3 (26·1–32·7; 29·5) | 29·0 (26·0–32·3; 29·3) | 29·3 (26·2–32·8; 29·5) |
| Race | | | | |
| White | 1216 (80%) | 1211 (79%) | 794 (81%) | 800 (80%) |
| Black | 14 (<1%) | 17 (1%) | 6 (<1%) | 7 (<1%) |
| Asian | 252 (16%) | 254 (17%) | 144 (15%) | 156 (16%) |
| Hawaiian/Islander | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| Other | 45 (3%) | 46 (3%) | 31 (3%) | 33 (3%) |
| History of venous thromboembolism | | | | |
| Deep vein thrombosis | 36 (2%) | 32 (2%) | 25 (3%) | 20 (2%) |
| Pulmonary embolism | 10 (<1%) | 10 (<1%) | 6 (<1%) | 6 (<1%) |
| Previous orthopaedic surgery | | | | |
| Knee replacement | 257 (17%) | 286 (19%) | 160 (16%) | 162 (16%) |
| Hip replacement | 90 (6%) | 80 (5%) | 55 (6%) | 60 (6%) |
| Hip or knee fracture surgery | 55 (4%) | 49 (3%) | 39 (4%) | 38 (4%) |
| Type of surgery | | | | |
| Unilateral, right | 759 (50%) | 747 (49%) | 511 (52%) | 513 (51%) |
| Unilateral, left | 687 (45%) | 714 (47%) | 441 (45%) | 463 (46%) |
| Bilateral | 31 (2%) | 30 (2%) | 24 (2%) | 21 (2%) |
| Type of anaesthesia | | | | |
| General | 540 (35%) | 548 (36%) | 377 (39%) | 374 (38%) |
| Spinal | 950 (62%) | 974 (64%) | 611 (63%) | 645 (65%) |
| Regional | 295 (19%) | 305 (20%) | 213 (22%) | 208 (21%) |
| Other | 77 (5%) | 72 (5%) | 52 (5%) | 52 (5%) |
| Duration of surgery (h) | 1·58 (1·25–2·00; 1·72) | 1·58 (1·25–2·00; 1·70) | 1·55 (1·25–2·00; 1·70) | 1·53 (1·22-2·00; 1·67) |
| Tourniquet use | 708 (46%) | 688 (45%) | 480 (49%) | 476 (48%) |
| Use of cement | 1387 (91%) | 1406 (92%) | 919 (94%) | 950 (95%) |
| Indication for surgery | | | | |
| Osteoarthritis | 970 (63%) | 960 (63%) | 605 (62%) | 633 (63%) |
| Degenerative joint disease | 346 (23%) | 333 (22%) | 229 (23%) | 213 (21%) |
| Rheumatoid arthritis | 57 (4%) | 77 (5%) | 41 (4%) | 39 (4%) |
| Other | 196 (13%) | 210 (14%) | 161 (16%) | 168 (17%) |
| Duration of hospital stay (days) | 12·0 (7–14; 11·5) | 12·0 (8–14; 11·7) | 12·0 (8–14; 11·4) | 12·0 (8–14; 11·8) |
| Region | | | | |
| South Africa | 56 (4%) | 56 (4%) | 35 (4%) | 32 (3%) |
| Europe | 1112 (73%) | 1110 (73%) | 737 (76%) | 745 (75%) |
| Latin America | 114 (7%) | 116 (8%) | 64 (7%) | 68 (7%) |
| Asia/Pacific | 246 (16%) | 247 (16%) | 140 (14%) | 152 (15%) |
| Renal status | | | | |
| Estimated creatinine clearance >60 mL/min | 1258 (82%) | 1291 (84%) | 820 (84%) | 858 (86%) |

Data are number (%) or median (IQR; mean). BMI=body-mass index.

***Table 1:*** **Baseline and other characteristics of patients allocated to treatment and primary efficacy population**

## Outcome measures

The primary outcome measure of efficacy was the composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death (all venous thromboembolism and all-cause death), with onset during the intended treatment period of 12 days (within 2 days) or within 2 days of last dose of study drug, whichever was longer. The main secondary outcome measure (major venous thromboembolism) was the composite of

| | Apixaban | | Enoxaparin | | Relative risk | p value | Absolute risk difference (%) |
|---|---|---|---|---|---|---|---|
| | n/N | Rate (%) | n/N | Rate (%) | | | |
| **During intended treatment** | | | | | | | |
| All venous thromboembolism and all-cause death* | 147/976 | 15·06% (12·95 to 17·46) | 243/997 | 24·37% (21·81 to 27·14) | 0·62 (0·51 to 0·74) | <0·0001 | –9·27% (–12·74 to –5·79) |
| Major venous thromboembolism† | 13/1195 | 1·09% (0·62 to 1·88) | 26/1199 | 2·17% (1·47 to 3·18) | 0·50 (0·26 to 0·97) | 0·0186 | –1·04% (–2·03 to –0·05) |
| Symptomatic venous thromboembolism or venous thromboembolism-related death‡ | 7/1528 | 0·46% (0·20 to 0·97) | 7/1529 | 0·46% (0·20 to 0·97) | 1·00 (0·35 to 2·85) | .. | 0·00% (–0·48 to 0·48) |
| All deep vein thrombosis§ | 142/971 | 14·6% (12·5 to 17·0) | 243/997 | 24·4% (21·8 to 27·1) | .. | .. | .. |
| Symptomatic deep vein thrombosis‡ | 3/1528 | 0·20% (0·04 to 0·61) | 7/1529 | 0·46% (0·20 to 0·97) | .. | .. | .. |
| Proximal deep vein thrombosis, symptomatic or asymptomatic¶ | 9/1192 | 0·76% (0·38 to 1·46) | 26/1199 | 2·17% (1·47 to 3·18) | .. | .. | .. |
| Pulmonary embolism, fatal or non-fatal‡ | 4/1528 | 0·26% (0·08 to 0·70) | 0/1529 | 0·00% (0·00 to 0·31) | .. | .. | .. |
| Pulmonary embolism, fatal‡ | 1 | .. | 0 | .. | .. | .. | .. |
| Death‡ | 2/1528 | 0·13% (0·01 to 0·52) | 0/1529 | 0·00% (0·00 to 0·31) | .. | .. | .. |
| **During intended follow-up for randomised patients who entered follow-up** | | | | | | | |
| Symptomatic deep vein thrombosis‡ | 2/1458 | 0·14% | 1/1469 | 0·07% | .. | .. | .. |
| Pulmonary embolism, fatal or non-fatal‡ | 3/1458‖ | 0·21% | 1/1469 | 0·07% | .. | .. | .. |
| Death‡ | 1/1458 | 0·07% | 1/1469 | 0·07% | .. | .. | .. |

Data are number, rate (95% CI), relative risk (95% CI), or absolute risk difference (95% CI). p values are one sided for superiority test of relative risk. All venous thromboembolism includes asymptomatic or symptomatic deep vein thrombosis, symptomatic deep vein thrombosis, or pulmonary embolism; major venous thromboembolism includes asymptomatic or symptomatic proximal deep vein thrombosis and non-fatal or fatal pulmonary embolism.*Patients randomly allocated to treatment who had an assessable bilateral venogram or who had adjudicated venous thromboembolism or who died from any cause. †Patients randomly allocated to treatment with a bilateral venogram that could be assessed for proximal deep vein thrombosis or who had proximal deep vein thrombosis or non-fatal or fatal pulmonary embolism. ‡All patients randomly allocated to treatment. §Patients randomly allocated to treatment who had an adjudicated and assessable bilateral venogram or an adjudicated deep vein thrombosis. ¶Patients randomly allocated to treatment who had an adjudicated bilateral venogram that could be assessed for proximal deep vein thrombosis or who had adjudicated proximal deep vein thrombosis. ||Including one fatal event.

***Table 2:*** **Efficacy outcomes**

adjudicated symptomatic or asymptomatic proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death during this period. The presence or absence of asymptomatic deep vein thrombosis at the end of the intended treatment period was assessed with bilateral venography[11] done between day 10 and day 14 (day 1 was the day of surgery). Clinically suspected deep vein thrombosis was confirmed or excluded with ultrasonography or venography, and suspected pulmonary embolism with ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography. In case of death, autopsy was done whenever possible.

Additional predefined adjudicated secondary efficacy outcomes during the intended treatment period were the composite of symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death; the composite of symptomatic or asymptomatic deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death (all deep vein thrombosis); components of all deep vein thrombosis, including symptomatic deep vein thrombosis, proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death; the composite of pulmonary embolism and venous thromboembolism-related death; venous thromboembolism-related death; and all-cause death. Secondary efficacy outcomes during the intended follow-up were symptomatic deep vein thrombosis, the composite of pulmonary embolism and venous thromboembolism-related death, and all-cause death.

The primary safety outcome was bleeding reported during treatment. Bleeding was assessed for discrete predefined categories of severity (major; clinically relevant non-major; minor; and the composite of major and clinically relevant non-major bleeding). The definition of major bleeding was adapted from the criteria for bleeding in non-surgical patients of the International Society of Thrombosis and Haemostasis.[12] Major bleeding was defined as acute clinically overt bleeding accompanied by one or more of the following: a decrease in blood haemoglobin concentration of 20 g/L or more during 24 h; transfusion of two or more units of packed red blood cells; critical site bleeding

| | Apixaban (n=1501) | Enoxaparin (n=1508) | Absolute risk difference | p value |
|---|---|---|---|---|
| Adjudicated major bleeding events* | 9 (0·6%; 0·30 to 1·16) | 14 (0·9%; 0·54 to 1·57) | –0·33% (–0·95 to 0·29) | 0·3014 |
| Diagnostic criteria for major bleeding | | | | |
| Clinically overt bleeding | 8 (0·5%) | 14 (0·9%) | .. | .. |
| Haemoglobin drop of 20 g/L or more within 24 h | 8 (0·5%) | 9 (0·6%) | .. | .. |
| Transfusion of two or more units of packed red blood cells | 5 (0·3%) | 9 (0·6%) | .. | .. |
| Bleeding at a critical site | | | | |
| Intracranial, intraspinal, intraocular, pericardial, intramuscular, retroperitoneal location, or fatal | 0 | 0 | .. | .. |
| Haemarthrosis | 1 (0·1%) | 2 (0·1%) | .. | .. |
| Other | 1 (0·1%) | 0 | .. | .. |
| Days from first dose of study drug to event | 2·2 (0·67) | 5·2 (4·64) | .. | .. |
| Bleeding at the surgical site based on investigator reports | | | | |
| All | 8 (0·5%) | 11 (0·7%) | .. | .. |
| Haematoma | 1 (0·1%) | 0 | .. | .. |
| Haemarthrosis | 0 | 4 (0·3%) | .. | .. |
| Haemarthrosis with intervention | 1 (0·1%) | 0 | .. | .. |
| Bruising or ecchymosis | 1 (0·1%) | 1 (0·1%) | .. | .. |
| Other surgical site bleeds (including overt and unknown) | 5 (0·3%) | 6 (0·4%) | .. | .. |
| Non-surgical bleeding events | | | | |
| All | 1 (0·1%) | 3 (0·2%) | .. | .. |
| Bruising or ecchymosis | 0 | 1 (0·1%) | .. | .. |
| Gastrointestinal | 1 (0·1%) | 2 (0·1%) | .. | .. |
| Adjudicated clinically relevant non-major bleeding† | 44 (2·9%; 2·19 to 3·93) | 58 (3·8%; 2·98 to 4·95) | –0·91% (–2·20 to 0·38) | 0·1668 |
| Days from first dose of study drug to event | 5·8 (4·04) | 4·8 (3·34) | .. | .. |
| Bleeding at the surgical site based on investigator reports | | | | |
| All | 32 (2·1%) | 44 (2·9%) | .. | .. |
| Haematoma | 13 (0·9%) | 11 (0·7%) | .. | .. |
| Haemarthrosis | 3 (0·2%) | 3 (0·2%) | .. | .. |
| Haemarthrosis with intervention | 1 (0·1%) | 0 | .. | .. |
| Bruising or ecchymosis | 6 (0·4%) | 10 (0·7%) | .. | .. |
| Other surgical site bleeds (including overt and unknown) | 9 (0·6%) | 20 (1·3%) | .. | .. |
| Non-surgical bleeding events | | | | |
| All | 12 (0·8%) | 16 (1·1%) | .. | .. |
| Haematoma | 3 (0·2%) | 3 (0·2%) | .. | .. |
| Bruising or ecchymosis | 3 (0·2%) | 3 (0·2%) | .. | .. |
| Epistaxis | 1 (0·1%) | 2 (0·1%) | .. | .. |
| Gastrointestinal | 2 (0·1%) | 2 (0·1%) | .. | .. |
| Haematuria | 2 (0·1%) | 5 (0·3%) | .. | .. |
| Haemoptysis | 1 (0·1%) | 1 (0·1%) | .. | .. |
| Adjudicated major or clinically relevant non-major bleeding events‡ | 53 (3·5%; 2·71 to 4·6) | 72 (4·8%; 3·81 to 5·98) | –1·24% (–2·66 to 0·18) | 0·0881 |
| Minor bleeding events | 51 (3·4%) | 54 (3·6%) | .. | .. |
| All bleeding events | 104 (6·9%; 5·75 to 8·34) | 126 (8·4%; 7·06 to 9·87) | –1·39% (–3·29 to 0·51) | 0·1412 |

Data are number (%; 95% CI), mean (SD), or % (95% CI). Absolute risk differences are adjusted for type of surgery. *Five patients in the apixaban group and five in the enoxaparin group had major bleeding events that occurred before the first postsurgery dose of study drug. †Seven patients in the apixaban group and 11 in the enoxaparin group had clinically relevant non-major bleeding events that occurred before the first postsurgery dose of study drug. ‡12 patients in the apixaban group and 16 in the enoxaparin group had major or clinically relevant non-major bleeding events that occurred before the first postsurgery dose of study drug.

***Table 3:*** **Bleeding events during treatment**

(including intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint needing reoperation or intervention; intramuscular bleeding with compartment syndrome; or fatal bleeding.

Clinically relevant non-major bleeding is defined in detail in the webappendix (p 1), and included acute clinically overt episodes such as wound haematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that did not meet criteria for major

| | Apixaban (n=1501) | | | Enoxaparin (n=1508) | | |
|---|---|---|---|---|---|---|
| | Treatment | Follow-up | Total | Treatment | Follow-up | Total |
| AT more than three times ULN | 25 (2%) | 2 (<1%) | 25 (2%) | 17 (1%) | 7 (<1%) | 23 (2%) |
| Total serum bilirubin more than two times ULN | 15 (<1%) | 3 (<1%) | 15 (<1%) | 8 (<1%) | 1 (<1%) | 8 (<1%) |
| AT more than three times ULN and bilirubin more than two times ULN on same date | 3 (<1%) | 1 (<1%) | 3 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| Thrombocytopenia | 0 | 1 (<1%) | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) |
| Myocardial infarction | 1 (<1%) | 0 | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) |
| Stroke | 2 (<1%) | 0 | 2 (<1%) | 0 | 0 | 0 |
| Serious adverse events* | 72 (5%) | 13 (<1%) | .. | 88 (6%) | 15 (<1%) | .. |

Data are number (%). AT=serum alanine aminotransferase and aspartate aminotransferase. ULN=upper limit of normal. Thrombocytopenia defined as a fall in platelet count to <100 000 per mm³ for patients with a postsurgery value of >150 000 per mm³ or a >50% decline if the baseline (postsurgery) value is ≤150 000 per mm³. *Number of patients with at least one serious adverse event.

***Table 4:*** **Summary of safety endpoints with onset during treatment and follow-up**

| | Apixaban (n=1501) | Enoxaparin (n=1508) |
|---|---|---|
| All AE | 786 (52%) | 836 (55%) |
| AE occurring in 5% or more of patients | | |
| Nausea | 102 (7%) | 120 (8%) |
| Vomiting | 77 (5%) | 88 (6%) |
| Constipation | 73 (5%) | 77 (5%) |
| Serious AE* | 72 (5%) | 88 (6%) |
| Drug-related serious AE* | 16 (1%) | 17 (1%) |
| Drug-related AE | 207 (14%) | 214 (14%) |
| Discontinuations due to AE | 40 (3%) | 44 (3%) |
| Bleeding AE | 90 (6%) | 112 (7%) |

Data are number (%). *No non-endpoint serious adverse events (AEs) occurred in 1% or more of patients.

***Table 5:*** **Adverse events reported by investigators during treatment (not including study endpoints)**

bleeding. Bleeding was regarded as minor if clinically overt but not adjudicated as major or clinically relevant non-major bleeding. Additional safety measures were rates of raised hepatic transaminase enzyme or bilirubin concentrations (measured at entry, four times during treatment, and twice during follow-up), thrombocytopenia, and arterial thromboembolism during treatment or follow-up (myocardial infarction, ischaemic stroke, other systemic thromboembolism).

### Statistical analysis

We postulated that apixaban was non-inferior to enoxaparin for the primary efficacy outcome using prespecified non-inferiority margins in which the upper limit of the 95% CI of the RR should not exceed 1·25, and for absolute risk difference the upper limit of the 95% CI should not exceed 5·6%. If both these criteria were met, then we planned a priori to test for superiority. If superiority was established for the primary efficacy outcome, then we planned a priori to test the secondary efficacy outcome for non-inferiority using a prespecified margin in which the upper limit of the 95% CI for RR should not exceed 1·5, and if this occurred to then test for superiority.

On the basis of previous studies, including the phase 2 study[13] of apixaban in knee replacement, we estimated primary efficacy outcome rates of 16% with enoxaparin and 11·2% with apixaban. If we accept a one-sided type 1 error of 0·025 and assume a 30% non-assessable venogram rate (as in previous studies),[3,5,13] a sample size of 3058 would provide power of 99% for the statistical test of non-inferiority with Yanagawa and colleagues' method,[14] and 90% for the test of superiority with the Mantel-Haenszel test. We used these methods to calculate RR and absolute risk difference adjusted by stratification for unilateral or bilateral surgery.

Primary efficacy analysis included data for all patients randomly allocated to treatment who had an assessable efficacy outcome (patients who, during the intended treatment period, had a venogram adjudicated as assessable, who developed confirmed deep vein thrombosis or pulmonary embolism, or who died from any cause); patients who had important protocol violations were excluded from the per-protocol analysis. For the secondary outcome of major venous thromboembolism, venogram results with assessable proximal venous segments were accepted irrespective of whether distal segments were readable. No interim analysis was done. The safety population was all patients allocated to treatment who received at least one dose of study drug. Differences in bleeding rates were analysed with the Mantel-Haenszel test. Other safety outcomes were analysed with appropriate descriptive methods. All p values reported for efficacy analyses were one sided; all p values reported for bleeding summaries were two sided. We used SAS (version 8.2) for all statistical analyses.

This study is registered at ClinicalTrials.gov, number NCT00452530.

### Role of the funding source

The study was sponsored by Bristol-Myers Squibb and Pfizer. Study design, protocol, and statistical plan were agreed between steering committee and sponsor, who obtained and analysed data. The steering committee decided to publish and wrote the report. All authors contributed to the report, had full access to data and analyses, and vouch for the report's accuracy and completeness.

## Results

Between June 29, 2007, and Nov 12, 2008, 3057 patients were randomly allocated to treatment from 125 sites in 27 countries (figure). Treatment groups had similar baseline demographic and clinical characteristics (table 1). Preoperative study drug injections were given

a mean 13·1 h (SD 1·9) before surgery, and first postoperative doses a mean 19·1 h (4·3) after wound closure in the apixaban group and 19·1 h (4·2) after wound closure in the enoxaparin group. Nine patients did not receive preoperative drugs. Mean duration of treatment was 12·1 days (3·2) for apixaban and 12·1 days (2·8) for enoxaparin. Investigators were able to assess venograms in similar proportions of both groups (figure).

Apixaban was superior to enoxaparin for prevention of the primary efficacy outcome, all venous thromboembolism and all-cause death (RR 0·62, 95% CI 0·51–0·74, one-sided p<0·0001 when tested for non-inferiority and for superiority; table 2). Absolute risk reduction was 9·3% (95% CI 5·8–12·7) in favour of apixaban (one-sided p<0·0001 for non-inferiority). Apixaban was also better than was enoxaparin for prevention of the secondary outcome, major venous thromboembolism (RR 0·50, 95% CI 0·26–0·97, one-sided p=0·0186 for superiority; absolute risk reduction 1·04%, 0·05–2·03; table 2). Rates of symptomatic venous thromboembolism and venous thromboembolism-related death did not differ between study groups (RR 1·00, 0·35–2·85; absolute risk reduction 0·00%, –0·48 to 0·48); one apixaban patient died of pulmonary embolism during treatment (table 2). 1458 (95%) of 1528 apixaban patients and 1469 (96%) of 1529 enoxaparin patients completed 60 days of follow-up after last dose of study drug. Symptomatic venous thromboembolism developed during follow-up in five (<1%) of 1458 apixaban patients and two (<1%) of 1469 enoxaparin patients.

Frequency of major bleeding events did not differ between treatment groups (table 3; webappendix p 2). Of nine major bleeding events with apixaban, five occurred before and four after the first dose. None were related to spinal or epidural anaesthesia. The composite outcome of major and clinically relevant non-major bleeding did not differ between groups (table 3). Liver transaminase concentrations were raised more than three times the upper limit of normal and bilirubin concentrations more than twice in small proportions of patients in each treatment group (table 4; webappendix p 3). Both events were reported on the same day of study therapy in one enoxaparin patient and three apixaban patients; one apixaban patient died.

Reports of adverse and serious adverse events during study therapy and follow-up were similar in each study group (table 5; webappendix p 3). Four patients died during treatment and follow-up (three allocated to receive apixaban and one enoxaparin). Pulmonary embolism was the adjudicated cause of death in two patients treated with apixaban (one on day 4 during treatment, one off study drug 45 days after surgery). For the third apixaban patient who died, study treatment was stopped on day 6 because of fever, jaundice, and raised liver transaminase and bilirubin concentrations; the adjudicated cause of death on day 12 was "query infection and hepatitis leading to aspiration pneumonia and multi-organ failure". Independent hepatologists masked to study treatment could not reach a diagnosis because of absence of autopsy or confirmed infectious organism, and a contribution by the study drug remains possible. The patient allocated to enoxaparin died with retroperitoneal bleeding 40 days after surgery while taking vitamin K antagonist for deep vein thrombosis.

## Discussion

Our results showed that postoperative apixaban, 2·5 mg twice daily, was more effective for prevention of venous thromboembolism than was enoxaparin, 40 mg per day, started before surgery, without increasing bleeding risk. The statistical analysis plan required demonstration of non-inferiority compared with enoxaparin, before testing for superiority. After this requirement was met, apixaban was most effective for prevention of the primary outcome of any venous thromboembolism and the predetermined and clinically more persuasive measure of major venous thromboembolism. Fewer major or clinically relevant non-major bleeding events occurred in the apixaban group than in the enoxaparin group, but the difference was not significant. By comparison, in ADVANCE-1 the efficacy of this apixaban regimen did not differ from that of twice daily 30 mg enoxaparin starting after surgery (venous thromboembolism in 9·0% *vs* 8·8% of 2287 patients), and major or clinically relevant non-major bleeding was reduced with apixaban.[10]

A feature of ADVANCE-2 and many similar studies is that patients are lost to efficacy analyses if their venography is suboptimum or not done (because of withdrawn consent or clinical or technical reasons).[5–8,13,15] In ADVANCE-2, 552 (36%) of 1528 and 532 (35%) of 1529 apixaban and enoxaparin patients (figure) could not be assessed for the primary efficacy outcome, compared with the projected 30%. This drawback is unlikely to undermine conclusions about relative efficacy. Probable rates of venous thromboembolism in patients who could not be assessed are unlikely to be unbalanced because their baseline demographics were similar between the two study groups, as were reasons for non-assessable venogram (figure), and randomisation was stratified by study centre to avoid imbalance. Crucially, our conclusions about major venous thromboembolism are likely to be robust since close to 75% of suboptimum venograms had interpretable proximal segments (figure), thus 1195 (78%) of 1528 of all apixaban and 1199 (78%) of 1529 of all enoxaparin patients allocated to treatment could be assessed for major venous thromboembolism. Furthermore, treatment allocation was masked to reduce ascertainment bias to a minimum, and the main

study findings are lent support by sensitivity analyses that modelled plausible outcome rates in patients with missing data.

To test for effect of site or country-specific variations in clinical care, we did statistical tests for non-inferiority and superiority on the primary and main secondary efficacy outcomes with effect of site as a covariate, and showed superiority for both. Within regions, relative effects of apixaban and enoxaparin on primary efficacy outcomes were consistent with the overall effect.

Effects on liver function are of special interest in view of previous findings with ximelagatran.[16] Few patients in either treatment group had raised transaminase enzyme or bilirubin concentrations during or after treatment. One multifactorial death after apixaban exposure was accompanied by abnormal results of liver tests, and a contribution by the study drug remains possible. Myocardial infarction or stroke during or after treatment was rare (<1%), as was venous thromboembolism-related death (two patients in the apixaban group during treatment or follow-up).

ADVANCE-1 and ADVANCE-2 compared the same apixaban regimen with different enoxaparin regimens (30 mg twice daily starting 12–24 h [average 20 h] after surgery in ADVANCE-1; 40 mg per day starting before surgery and resumed an average of 19 h after operation in ADVANCE-2). Whether enoxaparin timing and total daily dose are clinically important remains uncertain since head-to-head comparisons are scarce, but the indirect comparison that is made possible by the ADVANCE trials invites speculation that twice daily 30 mg enoxaparin could be more effective, but cause more bleeding (apixaban in ADVANCE-1 had clinically similar efficacy with reduced bleeding), whereas 40 mg per day enoxaparin could be less effective, but perhaps safer than is the twice daily dosage (in ADVANCE-2, apixaban was more effective without increased bleeding).

These favourable results might help surgeons to resolve their clinical dilemma when considering anticoagulant prophylaxis for total knee replacement. Bleeding can delay recovery and can predispose to infections that endanger the prosthesis. The small but occasionally important increase in surgical bleeding that is attributed to enoxaparin can contribute to underuse of effective prophylaxis.[17] In comparisons of new oral anticoagulants with enoxaparin (40 mg per day or 30 mg twice daily) in elective major joint replacement, anticoagulants have shown greater efficacy, but more bleeding,[18] greater efficacy with similar bleeding,[19] similar efficacy with similar bleeding,[6–8] or lower efficacy and similar bleeding risk compared with enoxaparin.[9] Therefore, the aim of similar or increased efficacy combined with reduced bleeding when compared with enoxaparin has not been achieved. By contrast, 2·5 mg apixaban twice daily, starting on the morning after total knee replacement, offers a convenient and more effective orally administered alternative to 40 mg per day enoxaparin, without increased bleeding.

#### Contributors

The authors met for 2 days to write the report, and contributed equally to all its components. Statistical analysis was provided by DC, as agreed at the meeting. The final submission and response to reviewers were agreed by teleconference. MRL was responsible for editorial correspondence.

#### Conflicts of interest

MRL has received consulting fees from Bristol-Myers Squibb, Pfizer, Bayer, Johnson & Johnson, GlaxoSmithKline, and Sanofi-Aventis. GER has received consulting fees from Bristol-Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Takeda, Johnson & Johnson, and Sanofi-Aventis. AG has received consulting fees from Bristol-Myers Squibb, Pfizer, Sanofi-Aventis, and Astellas. GP has received consulting fees from Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis. DC and PH are employees of and own stock in Bristol-Myers Squibb.

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