ORIGINAL ARTICLE

Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement

Michael Rud Lassen, M.D., Gary E. Raskob, Ph.D., Alexander Gallus, M.D., Graham Pineo, M.D., Dalei Chen, Ph.D., and Ronald J. Portman, M.D.

ABSTRACT

BACKGROUND

The optimal strategy for thromboprophylaxis after major joint replacement has not been established. Low-molecular-weight heparins such as enoxaparin predominantly target factor Xa but to some extent also inhibit thrombin. Apixaban, a specific factor Xa inhibitor, may provide effective thromboprophylaxis with a low risk of bleeding and improved ease of use.

METHODS

In a double-blind, double-dummy study, we randomly assigned patients undergoing total knee replacement to receive 2.5 mg of apixaban orally twice daily or 30 mg of enoxaparin subcutaneously every 12 hours. Both medications were started 12 to 24 hours after surgery and continued for 10 to 14 days. Bilateral venography was then performed. The primary efficacy outcome was a composite of asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause during treatment. Patients were followed for 60 days after anticoagulation therapy was stopped.

RESULTS

A total of 3195 patients underwent randomization, with 1599 assigned to the apixaban group and 1596 to the enoxaparin group; 908 subjects were not eligible for the efficacy analysis. The overall rate of primary events was much lower than anticipated. The rate of the primary efficacy outcome was 9.0% with apixaban as compared with 8.8% with enoxaparin (relative risk, 1.02; 95% confidence interval, 0.78 to 1.32). The composite incidence of major bleeding and clinically relevant nonmajor bleeding was 2.9% with apixaban and 4.3% with enoxaparin (P=0.03).

CONCLUSIONS

As compared with enoxaparin for efficacy of thromboprophylaxis after knee replacement, apixaban did not meet the prespecified statistical criteria for noninferiority, but its use was associated with lower rates of clinically relevant bleeding and it had a similar adverse-event profile. (ClinicalTrials.gov number, NCT00371683.)

From the Department of Orthopedics, Spine Clinic, Clinical Trial Unit, Hørsholm Hospital, University of Copenhagen, Hørsholm, Denmark (M.R.L.); the College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City (G.E.R.); SA Pathology at Flinders Medical Centre, and Flinders University, Adelaide, Australia (A.G.); the Department of Medicine and Oncology, University of Calgary, Calgary, AB, Canada (G.P.); and Research and Development, Bristol-Myers Squibb, Princeton, NJ (D.C., R.J.P.), for the Apixaban Dose Orally vs. Anticoagulant with Enoxaparin 2 (ADVANCE-1) Investigators. Address reprint requests to Dr. Lassen at Hørsholm Hospital, Department of Orthopedics, Spine Clinic, Clinical Trial Unit, Usserød Kongevej 102, DK-2970 Hørsholm, Denmark, or at mirula@noh.regionh.dk.

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The use of heparins, vitamin K antagonists, and mechanical methods to prevent venous thromboembolism after major joint surgery is now standard practice.[1] Despite effective prophylaxis, subclinical venous thrombosis develops soon after surgery in 15 to 20% of patients who undergo hip replacement and in 30 to 40% of those who undergo knee replacement[2]; symptomatic venous thromboembolism develops within 3 months after surgery in 2 to 4% of patients undergoing hip or knee replacement.[3,4]

Currently available prophylactic methods have practical limitations, since they require subcutaneous injection (the heparins) or careful dose adjustment (vitamin K antagonists) or tend to be cumbersome (mechanical devices). Recent clinical evaluations of orally active direct inhibitors of factor Xa[5,6] or thrombin[7,8] indicate that these new drugs (e.g., Xarelto [Bayer] and Pradaxa [Boehringer Ingelheim]) are no less effective for thromboprophylaxis after major joint surgery than low-molecular-weight heparins or vitamin K antagonists; they also have similar safety profiles and offer the advantage of greater ease of administration.

Apixaban is a potent, reversible, direct inhibitor of factor Xa.[9] In a phase 2 study,[10] the dose identified as appropriate for testing in phase 3 studies with patients undergoing major joint surgery was 2.5 mg twice daily. We report on the efficacy and safety of 2.5 mg of apixaban administered twice daily, started 12 to 24 hours after completion of surgery for elective total knee replacement and continued for 10 to 14 days. The postoperative regimen of 30 mg of enoxaparin every 12 hours was selected as the comparator because this regimen is approved by the Food and Drug Administration (FDA). Safety was of special importance, since the risk of bleeding could limit the use of apixaban.[11,12]

Methods

Patients

Patients were eligible to participate in the study if they were scheduled to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint. They were excluded if they had active bleeding or a contraindication to anticoagulant prophylaxis, or if they required ongoing anticoagulant or antiplatelet treatment. Additional exclusion criteria were uncontrolled hypertension, active hepatobiliary disease, clinically significant impairment of renal function, thrombocytopenia, anemia, allergy to heparin, and allergy to radiographic contrast dye or another contraindication to bilateral venography. A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design and Medications

We conducted a double-blind, double-dummy, randomized clinical trial. Potentially eligible patients were identified during a screening period of up to 30 days before surgery and randomly assigned to one of two study groups with the use of an interactive central telephone system. One group of patients received 2.5 mg of apixaban orally twice daily as well as an injection of placebo that mimicked injection with enoxaparin. The other group received 30 mg of enoxaparin subcutaneously every 12 hours along with placebo tablets that were identical in appearance to apixaban tablets. The randomization was stratified according to study site and whether a patient was undergoing replacement of one or both knees, with a block size of 4.

Patients received the first doses of the study medications 12 to 24 hours after surgery in order to be consistent with FDA label instructions for enoxaparin. Treatment was continued for 10 to 14 days, at which time mandatory bilateral venography was performed. All patients underwent a follow-up evaluation 30 days and 60 days after the last dose of study medication. After venography, continued prophylaxis or treatment for thrombosis was prescribed at the discretion of the investigator according to local practice. The trial was conducted in compliance with the Declaration of Helsinki. The protocol was approved by the ethics committee or institutional review board at each center, and written informed consent was obtained from each patient before randomization. All venograms and all episodes of suspected symptomatic venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia, or death were adjudicated, without knowledge of the patient's assigned treatment, by an independent central adjudication committee. The study was monitored by an independent data and safety monitoring board, which reviewed efficacy and

safety data at regular intervals. The chair of the board and board members received a fee for their professional service from the sponsors of the study.

The study was designed and supervised by the ADVANCE (Apixaban Dose Orally vs. Anticoagulation with Enoxaparin) steering committee (see the Supplementary Appendix for a list of committee members). Data were collected and analyzed by the study sponsors. The statistical-analysis plan was approved by the steering committee before the database was locked and unblinded. The steering committee also wrote the manuscript and made the decision to submit it for publication. All authors contributed to the writing of the manuscript and had full access to the data and analyses. The steering committee vouches for the accuracy and completeness of this report.

STUDY OUTCOMES

The primary efficacy outcome was the composite of adjudicated asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the intended treatment period. A secondary efficacy outcome was the composite of major thromboembolism (the composite of adjudicated proximal deep-vein thrombosis, nonfatal pulmonary embolism and VTE-related death) and death from any cause during the intended treatment period. Another secondary outcome was symptomatic thromboembolism (the composite of adjudicated symptomatic deep-vein thrombosis and nonfatal or fatal pulmonary embolism) during the intended treatment period. The presence or absence of deep-vein thrombosis was assessed with the use of bilateral venography[13] between day 10 and day 14. When deep-vein thrombosis was suspected on the basis of clinical information, ultrasonography or venography was used for confirmation. For suspected pulmonary embolism, the diagnosis was confirmed or ruled out with the use of ventilation–perfusion lung scanning, spiral computed tomography, or pulmonary angiography. For deaths, autopsy was performed whenever possible.

The primary safety outcome was bleeding during the treatment period or within 2 days after the last dose of study medication. Bleeding was evaluated according to discrete categories of severity defined before the study began, including major bleeding, clinically relevant nonmajor bleeding, minor bleeding, and the composite of major bleeding and clinically relevant nonmajor bleeding. The definition of major bleeding was adapted from the criteria of the International Society on Thrombosis and Haemostasis for bleeding in nonsurgical patients.[14] Major bleeding was defined as acute, clinically overt bleeding accompanied by one or more of the following events: a decrease in the hemoglobin level of 2 g per deciliter or more within a 24-hour period; a transfusion of 2 or more units of packed red cells; bleeding at a critical site (i.e., intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint, requiring an additional operation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. The definition of clinically relevant nonmajor bleeding is provided in the Supplementary Appendix; such bleeding included acute, clinically overt bleeding, such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis that did not meet the other criteria for major bleeding. The protocol specified an analysis of a composite of major and clinically relevant nonmajor bleeding. Bleeding was defined as minor if it was clinically overt but did not meet the criteria for either major or clinically relevant nonmajor bleeding. Additional safety outcomes were elevated aminotransferase or bilirubin levels and arterial thromboembolic events (myocardial infarction, acute ischemic stroke, or other systemic thromboembolism) occurring during the treatment period or during the 60-day follow-up period.

STATISTICAL ANALYSIS

The study plan was based on the hypothesis that apixaban would be noninferior to enoxaparin with respect to the primary efficacy outcome, with the use of a prespecified noninferiority margin in which the upper limit of the 95% confidence interval for relative risk did not exceed 1.25 and the upper limit of the 95% confidence interval for the difference in risk did not exceed 5.6 percentage points. Both criteria had to be met to establish noninferiority. We also planned to test for superiority if apixaban met the prespecified criteria for noninferiority. On the basis of previous studies,[10] the assumed incidences of the primary efficacy outcome were 16.0% for enoxaparin and 11.2% for apixaban. With these incidence data, a one-sided type I error of 0.025, and a 30% rate of venographic studies that could not be evaluated (based on the

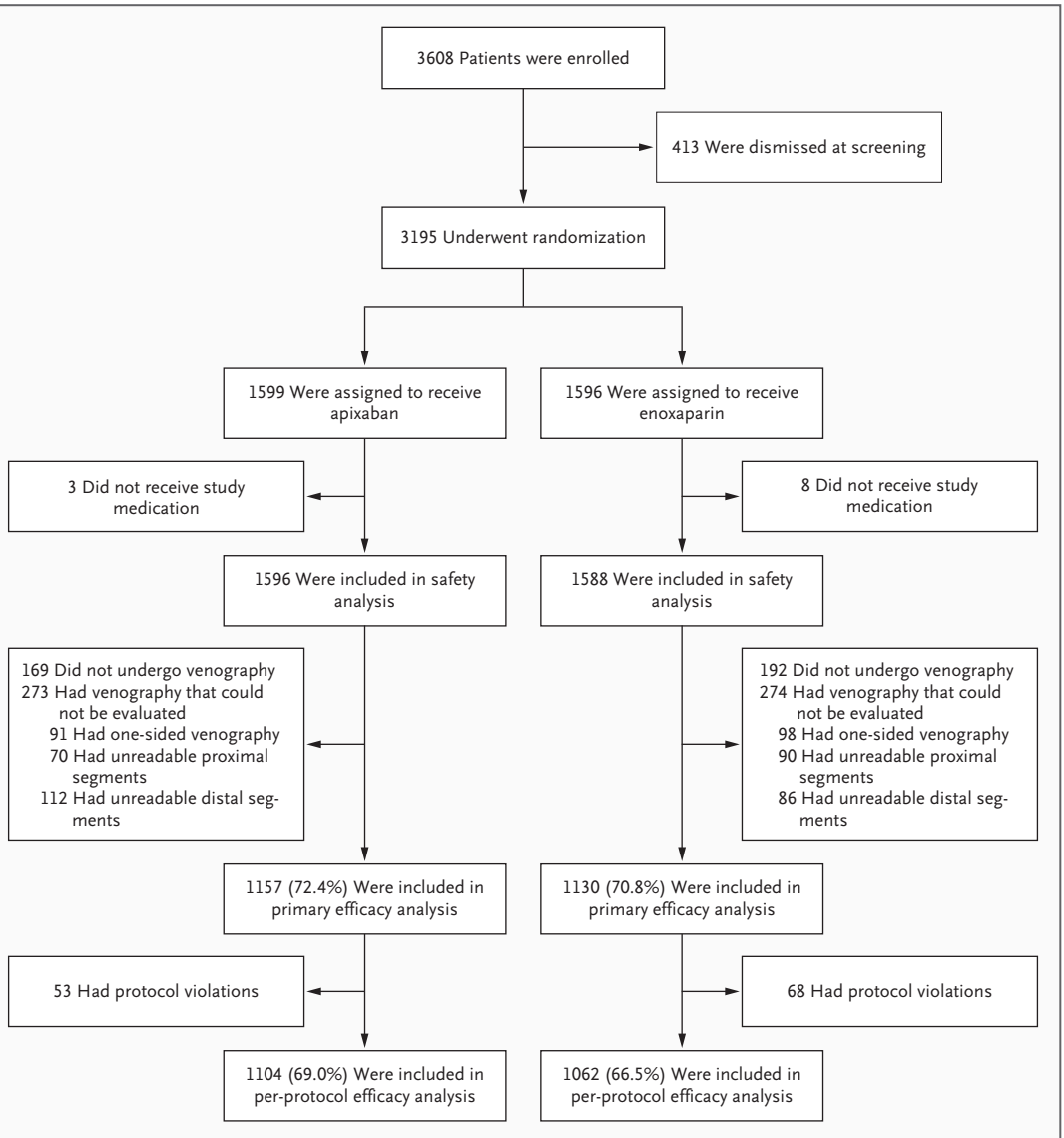

Figure 1. Enrollment and Randomization of Study Patients.
DVT denotes deep-vein thrombosis.

rates in other studies of venous thromboembolism[5,7,10]), we calculated that a sample of 3058 patients would provide 99% power for the statistical test of noninferiority according to the method of Yanagawa et al.[15] and would provide 90% power for the test of superiority with the use of the Mantel–Haenszel test. These methods were used to calculate the relative risk and difference in risk, adjusted according to the stratification for type of surgery (one knee vs. both knees).

The primary efficacy analysis was performed with the use of data from all patients who underwent randomization and who had an efficacy outcome that could be evaluated. Patients were included in the efficacy evaluation if they had a venogram that could be evaluated, as determined by the adjudication committee, if they had confirmed symptomatic deep-vein thrombosis or pulmonary embolism, or if they died from any cause during the intended treatment period. Symptoms suggesting venous thromboembolism were assessed in all patients who underwent randomization. For the secondary outcome of major venous thromboembolism and death from any cause, the

Table 1. Baseline Characteristics of the Patients.

Characteristic	Subjects Who Underwent Randomization		Subjects Eligible for Efficacy Analysis	
	Apixaban (N=1599)	Enoxaparin (N=1596)	Apixaban (N=1157)	Enoxaparin (N=1130)
Female sex — no. (%)	997 (62.4)	986 (61.8)	689 (59.6)	678 (60.0)
Age — yr				
Mean	65.9	65.7	66.1	65.5
Range	26–93	33–89	26–93	33–87
Weight — kg				
Mean	86.7	86.7	86.7	86.6
Range	41.0–163.7	40.5–163.3	46.5–163.7	40.5–163.3
Body-mass index*				
Mean	31.2	31.1	30.9	30.9
Range	18.1–54.7	17.7–57.6	18.1–54.7	17.7–51.6
Race — no. (%)†				
White	1515 (94.7)	1515 (94.9)	1108 (95.8)	1076 (95.2)
Black	63 (3.9)	58 (3.6)	33 (2.9)	34 (3.0)
Asian	9 (0.6)	16 (1.0)	7 (0.6)	14 (1.2)
Other	12 (0.8)	7 (0.4)	9 (0.8)	6 (0.5)
History of venous thromboembolism — no. (%)				
Deep-vein thrombosis	57 (3.6)	47 (2.9)	42 (3.6)	26 (2.3)
Pulmonary embolism	10 (0.6)	6 (0.4)	7 (0.6)	4 (0.4)
Previous orthopedic surgery — no. (%)				
Knee replacement	374 (23.4)	347 (21.7)	249 (21.5)	244 (21.6)
Hip replacement	91 (5.7)	73 (4.6)	65 (5.6)	47 (4.2)
Hip or knee fracture repair	65 (4.1)	62 (3.9)	46 (4.0)	43 (3.8)
Type of surgery — no. (%)				
Right side	802 (50.2)	782 (49.0)	588 (50.8)	555 (49.1)
Left side	763 (47.7)	779 (48.8)	548 (47.4)	548 (48.5)
Both sides	34 (2.1)	35 (2.2)	21 (1.8)	27 (2.4)
Type of anesthesia — no. (%)				
General	674 (42.2)	704 (44.1)	472 (40.8)	482 (42.7)
Spinal	947 (59.2)	920 (57.6)	696 (60.2)	673 (59.6)
Regional	440 (27.5)	462 (28.9)	332 (28.7)	340 (30.1)
Other	310 (19.4)	303 (19.0)	228 (19.7)	218 (19.3)
Duration of surgery — hr				
Mean	1.53	1.55	1.49	1.53
Range	0.45–13.90	0.08–4.72	0.45–13.90	0.08–4.72
Use of tourniquet — no. (%)	168 (10.5)	168 (10.5)	114 (9.9)	124 (11.0)
Use of cement — no. (%)	1513 (94.6)	1521 (95.3)	1096 (94.7)	1076 (95.2)

Table 1. (Continued.)

Characteristic	Subjects Who Underwent Randomization		Subjects Eligible for Efficacy Analysis	
	Apixaban (N=1599)	Enoxaparin (N=1596)	Apixaban (N=1157)	Enoxaparin (N=1130)
Indication for surgery — no. (%)				
Osteoarthritis	1291 (80.7)	1283 (80.4)	942 (81.4)	909 (80.4)
Degenerative joint disease	357 (22.3)	367 (23.0)	240 (20.7)	249 (22.0)
Rheumatoid arthritis	33 (2.1)	37 (2.3)	22 (1.9)	20 (1.8)
Other	82 (5.1)	84 (5.3)	53 (4.6)	58 (5.1)
Duration of hospitalization — days				
Mean	6.3	6.4	6.2	6.3
Range	2.0–37	2.0–67	2.0–37.0	3.0–46.0
Geographic region — no. (%)				
North America	1018 (63.7)	1022 (64.0)	755 (65.3)	739 (65.4)
Europe	308 (19.3)	300 (18.8)	227 (19.6)	217 (19.2)
Latin America	223 (13.9)	220 (13.8)	137 (11.8)	134 (11.9)
Asia and Pacific islands	50 (3.1)	54 (3.4)	38 (3.3)	40 (3.5)
Estimated creatinine clearance >60 ml/min — no. (%)	1388 (86.8)	1377 (86.3)	999 (86.3)	991 (87.7)

* The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was self-reported.

definition of a venogram that could be evaluated was modified to include all venograms with proximal venous segments that could be evaluated during the intended treatment period. Efficacy outcomes were also analyzed according to a prespecified per-protocol definition; the results of this analysis are included in the Supplementary Appendix. No interim analysis was performed for this study.

The population for analysis of safety included all patients who underwent randomization and received at least one dose of study medication. The differences in the incidences of bleeding were analyzed with the use of the Mantel–Haenszel test. The other safety outcomes were analyzed with the use of appropriate descriptive methods. All P values reported for the noninferiority analysis of the primary outcome and its components are one-sided, and all P values reported for bleeding are two-sided. All confidence intervals are two-sided, 95% intervals. To control for type I error, a sequential test procedure was performed to compare the efficacy of apixaban with that of enoxaparin for the primary efficacy outcome. The noninferiority of apixaban was tested first, with the plan that if noninferiority was demonstrated, the superiority of apixaban would be tested. Several sensitivity analyses were performed to evaluate the robustness of the data, taking into consideration the outcomes for patients that were outside the prespecified time for performance of venography and the outcomes for all randomized patients whose venograms could not be evaluated.

RESULTS

PATIENTS

The randomized population consisted of 3195 patients from 129 sites in 14 countries (Fig. 1). The demographic and clinical characteristics of the two treatment groups were similar at baseline (Table 1), and the results of venography were adequate in similar proportions of patients in the two groups (Fig. 1). The study medication was begun at a

mean (±SD) of 20.3±3.5 hours postoperatively in the apixaban group and at 20.2±3.7 hours in the enoxaparin group. The mean duration of treatment with study medication was 11.7±2.5 days in the apixaban group and 11.6±2.5 days in the enoxaparin group.

EFFICACY

The statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. The primary efficacy outcome occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (relative risk, 1.02; 95% confidence interval [CI], 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1 percentage point; 95% CI, –2.2 to 2.4; P <0.001). Table 2 lists the efficacy outcomes and their individual components. The results of the sensitivity analyses for the primary efficacy outcome are provided in the Supplementary Appendix.

The secondary outcome of major venous thromboembolism (the composite of adjudicated proximal deep-vein thrombosis, nonfatal pulmonary embolism, and VTE-related death) and death from any cause occurred in 26 of 1269 patients (2.1%) in the apixaban group and in 20 of 1216 patients (1.6%) in the enoxaparin group (relative risk, 1.25; 95% CI, 0.70 to 2.23; difference in risk, 0.36%; 95% CI, –0.68 to 1.40). Symptomatic venous thromboembolism (a composite of symptomatic deep-vein thrombosis and nonfatal or fatal pulmonary embolism) occurred in 19 of 1599 patients receiving apixaban (1.2%; 95% CI, 0.75 to 1.87) and 13 of 1596 patients receiving enoxaparin (0.81%; 95% CI, 0.46 to 1.41) (relative risk, 1.46; 95% CI, 0.72 to 2.95; difference in risk, 0.4 percentage point; 95% CI, –0.3 to 1.1). Follow-up for 60 days after the last dose of study medication was completed in 1562 of the 1599 patients (97.7%) assigned to apixaban and in 1554 of the 1596 patients (97.4%) assigned to enoxaparin. During the 60-day follow-up period, symptomatic venous thromboembolism occurred in 4 of 1562 patients (0.3%) in the apixaban group and in 7 of 1554 patients (0.5%) in the enoxaparin group.

SAFETY

Major bleeding events (Table 3) occurred in 11 of 1596 patients (0.7%) who received apixaban and in 22 of 1588 patients (1.4%) who received enoxaparin (adjusted difference in event rates according to type of surgery, –0.81%; 95% CI, –1.49 to –0.14%; P=0.053). The composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 46 patients (2.9%) in the apixaban group and 68 patients (4.3%) in the enoxaparin group (adjusted difference in event rates according to type of surgery, –1.46%; 95% CI, –2.75 to –0.17%; P=0.03).

With respect to other safety measures (Table 4), elevated aminotransferase or bilirubin levels were uncommon in both groups. The criteria for hepatotoxicity were not met in any patient receiving apixaban (95% CI for proportion of patients, 0 to 0.3%). Arterial thromboembolic events during the combined treatment and follow-up period occurred in two patients (0.1%) who received apixaban and in six patients (0.4%) who received enoxaparin. The incidences of reported adverse events and serious adverse events were similar in the two groups.

A total of nine patients died during the treatment and follow-up period (three in the apixaban group and six in the enoxaparin group). Pulmonary embolism was the adjudicated cause of death in four patients (two in each group).

DISCUSSION

Our first objective in conducting this study was to assess apixaban for noninferiority to enoxaparin as thromboprophylaxis in patients undergoing knee replacement. The prespecified noninferiority criteria were not met for the primary efficacy outcome — a composite of any venous thromboembolism plus death from any cause. This outcome was observed in 9.0% of patients who received apixaban and 8.8% of those who received enoxaparin. The assumptions made in establishing the criteria for noninferiority and calculating the sample size were based on previous clinical trials in which the adjudication of outcome events was consistent with ours and venous thromboembolism rates were about 16% in the control groups given enoxaparin every 12 hours after knee replacement.[10,16]

In our trial, the 8.8% incidence of the primary efficacy outcome in patients treated with enoxaparin was only 55% of the predicted rate. This result made it difficult to meet the prespecified criteria for noninferiority. The point estimate for the relative risk of the primary efficacy outcome was 1.02 (95% CI, 0.78 to 1.32); this 95% confidence interval indicates that a relative increase in risk with apixaban of more than 32% can be

Table 2. Efficacy Outcomes for Patients Who Underwent Randomization.*

Outcome	Patients with Events				Relative Risk (95% CI)	Difference in Risk (95% CI)
	Apixaban		Enoxaparin			
	no./total no. (%)	*95% CI*	*no./total no. (%)*	*95% CI*		
Intended treatment period						
All VTE and death from any cause	104/1157 (9.0)	7.47–10.79	100/1130 (8.8)	7.33–10.66	1.02 (0.78 to 1.32)	0.11 (–2.22 to 2.44)
Major VTE and death from any cause†	26/1269 (2.0)	1.39–3.01	20/1216 (1.6)	1.06–2.55	1.25 (0.70 to 2.23)	0.36 (–0.68 to 1.40)
Symptomatic VTE and VTE-related death	19/1599 (1.2)	0.75–2.95	13/1596 (0.8)	0.46–1.41	1.46 (0.72 to 2.95)	0.38 (–0.30 to 1.06)
All DVT‡	89/1142 (7.8)	6.37–9.51	92/1122 (8.2)	6.73–9.97		
Symptomatic DVT	3/1599 (0.2)	0.04–0.59	7/1596 (0.4)	0.20–0.93		
Proximal DVT§	9/1254 (0.7)	0.36–1.39	11/1207 (0.9)	0.49–1.65		
All pulmonary emboli	16/1599 (1.0)	0.61–1.64	7/1596 (0.4)	0.20–0.93		
Fatal	2/1599 (0.1)	0–0.49	0	0–0.30		
Death	3/1599 (0.2)	0.04–0.59	3/1596 (0.2)	0.04–0.59		
Intended Follow-up period						
Symptomatic DVT	3/1562 (0.2)	0.04–0.60	2/1554 (0.1)	0.01–0.51		
All pulmonary emboli	1/1562 (0.1)	0–0.41	5/1554 (0.3)	0.12–0.78		
Fatal	0	0–0.30	2/1554 (0.1)	0.01–0.51		
Death	0	0–0.30	3/1554 (0.2)	0.04–0.60		

* The total number is the number of patients who had a bilateral venogram that was deemed suitable for evaluation, had a VTE, or died from any cause. Each event was counted only once per subject, but subjects could be counted in multiple categories. Relative risk was calculated as the rate of efficacy for apixaban minus the rate of efficacy for enoxaparin divided by the rate of efficacy for enoxaparin. Difference in risk was calculated as the rate of efficacy for apixaban minus the rate of efficacy for enoxaparin. DVT denotes deep-vein thrombosis, and VTE venous thromboembolism.

† Major VTE was defined as proximal DVT, nonfatal pulmonary embolism, or fatal pulmonary embolism. The total number is the number of patients who had a bilateral proximal venogram that was deemed suitable for evaluation, had a major VTE, or died from any cause.

‡ The total number is the number of patients who had a bilateral venogram that was deemed suitable for evaluation or had a VTE.

§ The total number is the number of patients who had a bilateral proximal venogram that was deemed suitable for evaluation or had a proximal DVT.

plausibly ruled out. The 95% confidence interval for the difference of 0.1 percentage point between the primary-outcome rates in the apixaban and enoxaparin groups was –2.2% to 2.4%, making it unlikely that a true efficacy advantage of enoxaparin would exceed 2.4%. Given the advantage of apixaban with respect to the composite outcome of major bleeding and clinically relevant nonmajor bleeding, we conclude that our study shows that apixaban and enoxaparin have a similar efficacy that is within limits that should be acceptable to clinicians.

The inability to obtain venograms that can be evaluated for all patients is a practical limitation of this and other studies of thromboprophylaxis after major orthopedic surgery.[5-8,10,16-20] It is unlikely that rates of deep-vein thrombosis among the patients in our study who did not undergo venography would have differed between the two groups, since the study was randomized, with stratification according to study center, and we used a double-blind design. The rates of venographic studies that could be evaluated, the reasons for not performing venography, and the characteristics of the patients with venograms that could not be evaluated were similar in the two groups (Fig. 1). The sensitivity analyses of the data for the primary efficacy outcome support our conclusions about efficacy. Including the patients who underwent venography outside the allowed time window did not change the outcome.

The rates of symptomatic venous thromboembolism and related death were low both with apixaban and with enoxaparin (1.2% and 0.8%, respectively), although patients treated with apixaban had a higher rate of pulmonary embolism

Table 3. Summary of Bleeding Events That Occurred during the Treatment Period.*

Outcome	Apixaban (N=1596)		Enoxaparin (N=1588)		Difference in Risk (95% CI)	P Value
	no. (%)	*95% CI*	*no. (%)*	*95% CI*		
Adjudicated major bleeding events	11 (0.7)	0.4–1.3	22 (1.4)	0.9–2.1	–0.81 (–1.49 to 0.14)	0.05
Days from first dose of study drug to event	3.3±3.47		3.9±3.52			
Diagnostic criteria for major bleeding event						
Clinically overt bleeding	10 (0.6)		22 (1.4)			
Decrease in hemoglobin of ≥2 g/dl within 24 hr	10 (0.6)		16 (1.0)			
Transfusion of ≥2 units of packed red cells	9 (0.6)		18 (1.1)			
Bleeding at a critical site						
Intracranial bleeding	0		1 (<0.1)			
Bleeding from any intraspinal, intraocular, pericardial, intramuscular, or retroperitoneal location	0		0			
Fatal bleeding	0		1 (<0.1)			
Hemarthrosis	1 (<0.1)		4 (0.3)			
Other	3 (0.2)		5 (0.3)			
Bleeding at surgical site†						
Total	8 (0.5)		14 (0.9)			
Hematoma	2 (0.1)		2 (0.1)			
Hemarthrosis	0		3 (0.2)			
Hemarthrosis with intervention	0		2 (0.1)			
Bruising or ecchymosis	1 (<0.1)		1 (0.1)			
Other surgical site	5 (0.3)		7 (0.4)			
Nonsurgical bleeding events	3 (0.2)		10 (0.6)			
Total						
Bruising or ecchymosis	0		1 (<0.1)			
Intracranial hemorrhage	0		1 (<0.1)			
Gastrointestinal bleeding	1 (<0.1)		6 (0.4)			
Other	2 (0.1)		2 (0.1)			
Adjudicated clinically relevant nonmajor bleeding events	35 (2.2)	1.6–3.1	47 (3.0)	2.2–3.4	–0.77 (–1.87 to 0.33)	
Days from first dose of study drug to event	4.3±3.69		4.3±3.19			
Bleeding at surgical site†						
Total	22 (1.4)		35 (2.2)			
Hematoma	7 (0.4)		16 (1.0)			
Hemarthrosis	2 (0.1)		2 (0.1)			
Hemarthrosis with intervention	1 (<0.1)		0			
Bruising or ecchymosis	7 (0.4)		10 (0.6)			
Other	7 (0.4)		11 (0.7)			
Nonsurgical bleeding events						
Total	13 (0.8)		11 (0.7)			
Hematoma	1 (<0.1)		2 (0.1)			
Bruising or ecchymosis	6 (0.4)		2 (0.1)			
Epistaxis	1 (<0.1)		1 (<0.1)			
Gastrointestinal	0		4 (0.3)			
Other	5 (0.3)		3 (0.2)			

Table 3. (Continued.)

	Apixaban (N=1596)		Enoxaparin (N=1588)		Difference in Risk (95% CI)	P Value
	no. (%)	*95% CI*	*no. (%)*	*95% CI*		
Adjudicated major or clinically relevant nonmajor bleeding events	46 (2.9)	2.2–3.8	68 (4.3)	3.4–5.4	–1.46 (–2.75 to 0.17)	0.03
All bleeding events	85 (5.3)	4.3–6.6	108 (6.8)	5.7–8.2	–1.52 (–3.18 to 0.13)	0.08
Minor bleeding events	39 (2.4)		40 (2.5)			

* All data are numbers and percentages of patients except for days from first dose of study drug to event, which are given as means ±SD. There may have been more than one bleeding event per patient; thus, the total number of bleeding events may be greater than the total number of patients with major or clinically relevant nonmajor bleeding.
† Numbers are from investigator reports.

Table 4. Summary of Safety Outcomes during the Intended Treatment and Follow-up Periods.*

Outcome	Apixaban, 2.5 mg Twice Daily (N=1596)			Enoxaparin, 30 mg Every 12 Hr (N=1588)		
	Treatment Period	Follow-up Period	Total	Treatment Period	Follow-up Period	Total
	number (percent)					
AT >3 times ULN on same date	16 (1.0)	2 (0.1)	18 (1.1)	25 (1.6)	3 (0.2)	27 (1.7)
Total serum bilirubin >2 times ULN	2 (0.1)	1 (<0.1)	2 (0.1)	8 (0.5)	0	8 (0.5)
AT >3 times ULN and bilirubin >2 times ULN on same date	0	0	0	2 (0.1)	0	2 (0.1)
Thrombocytopenia†	0	0	0	2 (0.1)	0	2 (0.1)
Myocardial infarction	1 (<0.1)	1 (<0.1)	2 (0.1)	4 (0.3)	1 (<0.1)	5 (0.3)
Stroke	0	0	0	2 (0.1)	0	2 (0.1)
One or more serious adverse events	123 (7.7)	14 (0.9)	135 (8.5)	123 (7.7)	15 (0.9)	136 (8.6)

* AT denotes serum alanine aminotransferase and aspartate aminotransferase, and ULN upper limit of the normal range.
† Thrombocytopenia was defined as a decline in the platelet count to less than 100,000 per cubic millimeter for subjects with a postsurgery value of more than 150,000 per cubic millimeter or more than a 50% decline if the baseline (postsurgery) value was 150,000 per cubic millimeter or less.

(1.0% vs. 0.4%). These differences could have occurred by chance. Data from the two ongoing phase 3 studies of the use of apixaban after major joint surgery may provide further insight into this observation.

The risk of bleeding is a critical issue for surgeons and their patients. The apixaban regimen was associated with a lower risk of major bleeding (P=0.053) and with a lower risk of major and nonmajor clinical bleeding, as compared with the enoxaparin regimen (P=0.03).

The rates of death and symptomatic venous thromboembolism were higher during the 2-month follow-up period after the end of active prophylaxis among patients who received enoxaparin than among those who received apixaban. Consequently, the cumulative number of patients who had symptomatic venous thromboembolism or who died was similar in the two treatment groups by the end of the study period. There was no sign of hepatic toxic effects and no evidence of an increase in the risk of arterial thromboembolism in either group during treatment or the follow-up period.[17,18]

In interpreting differences in outcome rates among clinical trials, it is prudent to allow for the possibility of an influence by the adjudicating team. We therefore relied on the previous experience of the same team used during the phase 2 program when projecting a probable rate of venous thromboembolism in the enoxaparin group of 16%. We cannot explain why the rate was 8.8% in our study,

but rates of close to 10% were recorded with the use of enoxaparin every 12 hours after knee replacement in two recent trials that also evaluated a new anticoagulant and engaged the same adjudication team.[19,20] A plausible explanation is that rates of postoperative thrombosis rates are decreasing, perhaps because of improved anesthetic and surgical techniques and patient care, including encouraging patients to walk much sooner after surgery than had previously been the case.[21,22]

Our results support the view that specific factor Xa inhibition has the potential to combine effective thromboprophylaxis with a low risk of bleeding and may have a favorable benefit-to-risk ratio as compared with that for low-molecular-weight heparins.

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