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Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement

Michael Rud Lassen, M.D., Alexander Gallus, M.D., Gary E. Raskob, Ph.D., Graham Pineo, M.D., Dalei Chen, Ph.D., and Luz Margarita Ramirez, M.D., for the ADVANCE-3 Investigators*

ABSTRACT

BACKGROUND

There are various regimens for thromboprophylaxis after hip replacement. Low-molecular-weight heparins such as enoxaparin predominantly inhibit factor Xa but also inhibit thrombin to some degree. Orally active, specific factor Xa inhibitors such as apixaban may provide effective thromboprophylaxis with a lower risk of bleeding and improved ease of use.

METHODS

In this double-blind, double-dummy study, we randomly assigned 5407 patients undergoing total hip replacement to receive apixaban at a dose of 2.5 mg orally twice daily or enoxaparin at a dose of 40 mg subcutaneously every 24 hours. Apixaban therapy was initiated 12 to 24 hours after closure of the surgical wound; enoxaparin therapy was initiated 12 hours before surgery. Prophylaxis was continued for 35 days after surgery, followed by bilateral venographic studies. The primary efficacy outcome was the composite of asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the treatment period. Patients were followed for an additional 60 days after the last intended dose of study medication.

RESULTS

A total of 1949 patients in the apixaban group (72.0%) and 1917 patients in the enoxaparin group (71.0%) could be evaluated for the primary efficacy analysis. The primary efficacy outcome occurred in 27 patients in the apixaban group (1.4%) and in 74 patients in the enoxaparin group (3.9%) (relative risk with apixaban, 0.36; 95% confidence interval [CI], 0.22 to 0.54; P<0.001 for both noninferiority and superiority; absolute risk reduction, 2.5 percentage points; 95% CI, 1.5 to 3.5). The composite outcome of major and clinically relevant nonmajor bleeding occurred in 129 of 2673 patients assigned to apixaban (4.8%) and 134 of 2659 assigned to enoxaparin (5.0%) (absolute difference in risk, −0.2 percentage points; 95% CI, −1.4 to 1.0).

CONCLUSIONS

Among patients undergoing hip replacement, thromboprophylaxis with apixaban, as compared with enoxaparin, was associated with lower rates of venous thromboembolism, without increased bleeding. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00423319.)

From the Department of Orthopedics, Spine Clinic, and Clinical Trial Unit, Hørsholm Hospital, University of Copenhagen, Hørsholm, Denmark (M.R.L.); SA Pathology at Flinders Medical Centre, and Flinders University, Adelaide, SA, Australia (A.G.); the College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City (G.E.R.); the Departments of Medicine and Oncology, University of Calgary, Calgary, AB, Canada (G.P.); and Research and Development, Bristol-Myers Squibb, Princeton, NJ (D.C., L.M.R.). 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.

*The Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 3 (ADVANCE-3) trial investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Patients undergoing hip-replacement surgery require effective thromboprophylaxis, and low-molecular-weight heparins, vitamin K antagonists, and mechanical methods are now standard therapies. Despite prophylaxis, however, subclinical deep-vein thrombosis develops in approximately 15 to 20% of patients soon after surgery, and symptomatic venous thromboembolism develops in 2 to 4% during the first 3 months after surgery.[1]

Practical limitations of current prophylactic techniques have stimulated a search for simpler methods. Low-molecular-weight heparins and fondaparinux require subcutaneous injection. Warfarin has a delayed onset of action and is relatively ineffective soon after surgery. Mechanical methods are cumbersome and relatively ineffective after hip surgery.

The development of new oral anticoagulant agents has raised hopes that they will combine greater convenience with efficacy and safety profiles that are similar to or better than those of other methods. The use of rivaroxaban, a factor Xa inhibitor, and dabigatran etexilate, a direct thrombin inhibitor, for the prevention of venous thromboembolism after joint-replacement surgery has been evaluated in several phase 3 clinical trials.[2-8]

Apixaban is a highly specific factor Xa inhibitor that is administered in a fixed dose twice a day and does not require routine laboratory monitoring.[9] Clinical trials of apixaban involving patients who have undergone elective knee-replacement surgery showed that, as compared with enoxaparin, apixaban had better efficacy, with a similar or lower risk of bleeding.[10-12] We conducted a randomized, phase 3 study, the Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism 3 (ADVANCE-3) trial, to compare apixaban with enoxaparin in patients undergoing elective total hip replacement. Both drugs were continued for 35 days after surgery.

METHODS

PATIENTS

Patients were eligible if they were scheduled to undergo elective total hip replacement or revision of a previously inserted hip prosthesis. Major exclusion criteria were active bleeding, a contraindication to anticoagulant prophylaxis, or the need for ongoing anticoagulant or antiplatelet treatment. (A complete list of exclusion criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STUDY DESIGN AND OVERSIGHT

The study was a randomized, double-blind, double-dummy clinical trial. Potentially eligible patients were identified during a screening period of up to 14 days before surgery and were randomly assigned, with the use of an interactive telephone system, to receive apixaban at a dose of 2.5 mg orally twice daily plus placebo injections once daily or enoxaparin at a dose of 40 mg subcutaneously once daily plus placebo tablets twice daily. The randomization schedule was generated at the randomization center of Bristol-Myers Squibb with the use of SAS software and was stratified according to study site, with a block size of four. The study protocol, including the statistical analysis plan, is available at NEJM.org.

The study was designed and supervised by the ADVANCE-3 trial steering committee (see the Supplementary Appendix for a list of committee members) and was funded by Bristol-Myers Squibb and Pfizer. The protocol was approved by the ethics committee or institutional review board at each participating center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided written informed consent before enrollment. An independent data and safety monitoring board regularly reviewed efficacy and safety data; the members of this board received a fee from the sponsors for professional services. The data were collected and analyzed by the study sponsors. The steering committee approved the statistical analysis plan before the database was locked, had full access to the data and analyses, collectively wrote the first and later drafts of the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the reported data and the fidelity of this report to the study protocol.

STUDY MEDICATIONS AND ASSESSMENTS

Administration of the subcutaneous study medication (enoxaparin or placebo) was to be initiated 12 hours (plus or minus 3 hours) before surgery and continued after surgery according to the investigator's standard of care. The first dose of the oral study medication (apixaban or placebo) was given 12 to 24 hours after closure of the surgical wound. There were no restrictions on diet or the timing of meals relative to taking the oral study

medications. Devices used in connection with intrathecal or epidural anesthesia were removed at least 5 hours before the first postoperative dose of oral study medication was administered. Study medications were continued for 32 to 38 days, after which mandatory bilateral venography was performed.[13] All patients underwent a follow-up evaluation 65 days (plus or minus 5 days) and 95 days (plus or minus 5 days) after surgery.

During the time they were in the hospital, all the patients were assessed daily for symptomatic deep-vein thrombosis and pulmonary embolism, bleeding, and wound complications. Objective tests were performed in patients with clinically suspected venous thromboembolism to confirm or rule out the diagnosis. All thromboembolic events that were detected were managed according to local practice. In the case of death, an autopsy was performed whenever possible. All venograms and all episodes of suspected symptomatic venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia, and death were adjudicated by an independent central adjudication committee whose members were unaware of the treatment assignments.

OUTCOME MEASURES

The primary efficacy outcome was the composite of adjudicated asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the intended treatment period (i.e., from randomization to day 32 to 38 or to within 2 days after the last dose of study medication was administered, whichever was longer). The secondary efficacy outcome — major venous thromboembolism — was the composite of adjudicated symptomatic or asymptomatic proximal deep-vein thrombosis (popliteal, femoral, or iliac-vein thrombosis), nonfatal pulmonary embolism, or death related to venous thromboembolism, during the same period.

The primary safety outcome was bleeding during the treatment period or until 2 days after the last dose of study medication was administered. Bleeding was categorized a priori as major, clinically relevant nonmajor, or minor bleeding and as the composite of major and clinically relevant nonmajor bleeding. The definition of major bleeding[14] was acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. Clinically relevant nonmajor bleeding included acute, clinically overt episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis that did not meet the criteria for major bleeding (see the Supplementary Appendix). Bleeding was categorized as minor if it was clinically overt but was not adjudicated as major or clinically relevant nonmajor bleeding. Additional safety measures were elevated levels of hepatic aminotransferase enzymes or bilirubin, thrombocytopenia, and arterial thromboembolism (myocardial infarction, stroke, or other systemic thromboembolism) during the treatment or follow-up period.

STATISTICAL ANALYSIS

We tested the hypothesis that apixaban would be noninferior to enoxaparin with respect to the primary efficacy outcome, using prespecified noninferiority margins in which the maximum value for the upper limit of the 95% confidence interval for relative risk was 1.25. If noninferiority was established for the primary efficacy outcome, the secondary efficacy outcome would be tested for noninferiority with the use of a prespecified margin in which the maximum value for the upper limit of the 95% confidence interval for relative risk was 1.5. Finally, if apixaban met the prespecified criteria for noninferiority with respect to both the primary and secondary efficacy outcomes, we would test for superiority using Pearson's chi-square test. This sequential testing procedure maintained the one-sided alpha level at 0.025.

We estimated that assigning 4022 patients in a 1:1 ratio to apixaban or enoxaparin would give the study 92% power to establish noninferiority with respect to the primary efficacy outcome (one-sided alpha of 0.025), assuming true event rates of 3.85% with apixaban and 5.50% with enoxaparin, and 80% power to establish noninferiority with respect to the secondary efficacy outcome (one-sided alpha of 0.025). Our calculations assumed the use of the Farrington–Manning test for noninferiority,[15] as well as a 30% rate of venograms that could not be evaluated for total deep-vein thrombosis and a 20% rate of venograms that could not be evaluated for proximal deep-vein thrombosis. The protocol prespecified a review of

aggregate event rates for primary and secondary efficacy outcomes, with treatment assignments concealed, after 80% of the patients had been randomly assigned to a group, to permit an increase in the sample size if a larger size was needed to achieve adequate power for testing noninferiority of the primary efficacy outcome. When this review was performed, the aggregate primary event rate was 3.3%; therefore, the sample was increased to 5406 patients in order to maintain 90% power to establish noninferiority for the primary efficacy outcome (one-sided alpha of 0.025), assuming true event rates of 2.72% in the apixaban group and 3.88% in the enoxaparin group. The new sample size also provided 66% power to establish noninferiority with respect to the secondary efficacy outcome (one-sided alpha of 0.025).

The primary efficacy analysis was performed on data from all patients who underwent randomization and who had a primary efficacy outcome that could be evaluated. For the secondary efficacy outcome of major venous thromboembolism, patients for whom proximal venous segments were adequately visualized on the venogram were included in the analysis, regardless of whether distal segments could be evaluated. The safety analysis included all patients who underwent randomization and who received at least one dose of the study medication. Differences in bleeding rates were analyzed with the use of the Mantel–Haenszel test. Appropriate descriptive methods were used for other safety outcomes.

All P values reported for noninferiority tests on primary and key secondary end points are based on one-sided tests. All other reported P values are based on two-sided tests.

RESULTS

PATIENTS

Between March 2007 and May 2009, a total of 5407 patients from 160 sites in 21 countries underwent randomization (Fig. 1). The baseline demographic and clinical characteristics of all the patients who underwent randomization and of all the patients who could be evaluated for the primary efficacy outcome were similar between the study groups (Table 1). The preoperative injection of the study drug was given a mean (±SD) of 13.6±2.1 hours before surgery in both groups. The preoperative injection was not given to 14 of the 2673 patients in the apixaban group (0.5%) and 15 of the 2659 patients in the enoxaparin group (0.6%). The first postoperative dose of study medication was given 19.0±4.6 and 18.9±4.6 hours after closure of the surgical wound in the apixaban and enoxaparin groups, respectively. Mean adherence to the study medication was greater than 99% in both treatment groups (see the Supplementary Appendix). The mean duration of treatment was 34.0±7.7 days in the apixaban group and 33.9±7.8 days in the enoxaparin group. Among the 5332 patients who received at least one dose of the study medication, 3174 (59.5%) received nonsteroidal antiinflammatory drugs, and 622 (11.7%) received aspirin at least once during the treatment period. The proportion of venograms that could be evaluated was similar in the two treatment groups (Fig. 1).

EFFICACY

The primary efficacy outcome occurred in 27 of the 1949 patients in the apixaban group who could be evaluated for that outcome (1.4%) and in 74 of the 1917 patients in the enoxaparin group who could be evaluated (3.9%) (relative risk with apixaban, 0.36; 95% confidence interval [CI], 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority) (Table 2). The absolute risk reduction with apixaban was 2.5 percentage points (95% CI, 1.5 to 3.5).

Major venous thromboembolism occurred in 10 of the 2199 patients (0.5%) in the apixaban group who could be evaluated for that outcome and in 25 of the 2195 (1.1%) in the enoxaparin group (relative risk, 0.40; 95% CI, 0.15 to 0.80; one-sided P<0.001 for noninferiority and two-sided P=0.01 for superiority) (Table 2). The absolute risk reduction with apixaban was 0.7 percentage points (95% CI, 0.2 to 1.3). With this reduction in risk, one additional episode of major venous thromboembolism would be prevented for every 147 patients treated with apixaban rather than enoxaparin. Incidences of the composite outcome of symptomatic venous thromboembolism or death related to venous thromboembolism and the separate outcomes of symptomatic venous thromboembolism, proximal deep-vein thrombosis, pulmonary embolism, and death are shown in Table 2.

A total of 2598 patients in the apixaban group (95.9%) and 2577 patients in the enoxaparin group (95.5%) completed the follow-up evaluation 60 days after the last dose of study medication was

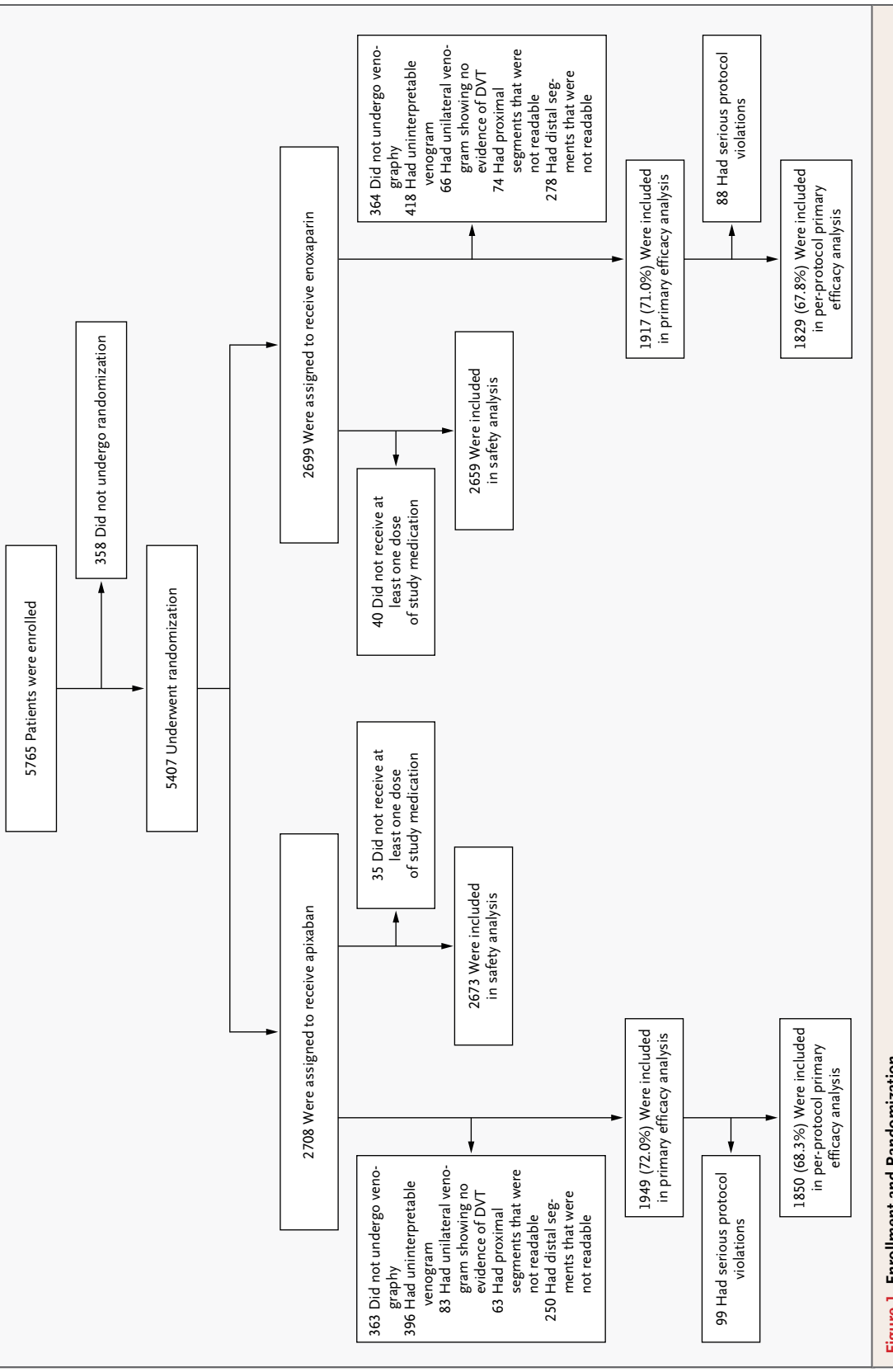

Figure 1. Enrollment and Randomization.

Patients who received at least one dose of study medication were included in the safety analysis. The primary efficacy analysis included all patients who underwent randomization and who had a primary efficacy outcome that could be evaluated. In the case of patients who were not included in the primary efficacy analysis because they did not undergo venography, either venography was not performed at all or it was performed outside the intended treatment period. The per-protocol efficacy analysis excluded patients with relevant protocol violations. DVT denotes deep-vein thrombosis.

administered. Symptomatic venous thromboembolism or death related to venous thromboembolism during the follow-up period occurred in none of the patients in the apixaban group and in 6 patients (0.2%) in the enoxaparin group.

SAFETY

Major bleeding during the treatment period occurred in 22 of the 2673 patients who received apixaban (0.8%) and 18 of the 2659 patients who received enoxaparin (0.7%) (absolute difference

Table 1. Baseline and Other Characteristics of the Study Patients.

Characteristic	Patients Who Underwent Randomization		Patients Included in the Primary Efficacy Analysis*		
	Apixaban (N=2708)	Enoxaparin (N=2699)	Apixaban (N=1949)	Enoxaparin (N=1917)	P Value†
Female sex — no. (%)	1430 (52.8)	1451 (53.8)	1024 (52.5)	1005 (52.4)	0.94
Age — yr					0.08
Mean	60.9	60.6	60.7	60.0	
Range	19–92	19–93	19–90	19–91	
Weight — kg					0.64
Mean	79.9	79.5	79.9	79.6	
Range	37.0–179.9	28.0–152.4	41.0–144.7	39.9–149.0	
Body-mass index‡					0.64
Mean	28.2	28.1	28.1	28.0	
Range	15.4–58.5	12.5–48.7	15.4–58.5	16.1–48.6	
Race or ethnic group — no. (%)§					0.94
White	2451 (90.5)	2446 (90.6)	1789 (91.8)	1769 (92.3)	
Black	69 (2.5)	63 (2.3)	43 (2.2)	39 (2.0)	
American Indian or Alaska Native	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0)	
Asian	182 (6.7)	188 (7.0)	115 (5.9)	108 (5.6)	
Hawaiian or Pacific Islander	1 (<0.1)	0	0	0	
Other	3 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	
History of venous thromboembolism — no. (%)					
Deep-vein thrombosis	41 (1.5)	47 (1.7)	26 (1.3)	33 (1.7)	0.33
Pulmonary embolism	17 (0.6)	11 (0.4)	14 (0.7)	9 (0.5)	0.31
Previous orthopedic surgery — no. (%)					
Knee replacement	124 (4.6)	116 (4.3)	85 (4.4)	73 (3.8)	0.39
Hip replacement	624 (23.0)	623 (23.1)	452 (23.2)	421 (22.0)	0.36
Surgery to repair hip or knee fracture	194 (7.2)	195 (7.2)	124 (6.4)	139 (7.3)	0.27
Current hip replacement¶					
Type of surgery— no./total no. (%)					0.22
Unilateral, right	1430/2673 (53.5)	1386/2659 (52.1)	1057/1949 (54.2)	1002/1917 (52.3)	
Unilateral, left	1220/2673 (45.6)	1257/2659 (47.3)	892/1949 (45.8)	915/1917 (47.7)	
Type of anesthesia — no./total no. (%)					
General	1052/2673 (39.4)	1073/2659 (40.4)	737/1949 (37.8)	752/1917 (39.2)	0.37
Spinal	1636/2673 (61.2)	1593/2659 (59.9)	1235/1949 (63.4)	1189/1917 (62.0)	0.39
Regional	186/2673 (7.0)	208/2659 (7.8)	141/1949 (7.2)	148/1917 (7.7)	0.57
Other	204/2673 (7.6)	221/2659 (8.3)	154/1949 (7.9)	155/1917 (8.1)	0.83

Table 1. (Continued.)

Characteristic	Patients Who Underwent Randomization		Patients Included in the Primary Efficacy Analysis*		
	Apixaban (N=2708)	Enoxaparin (N=2699)	Apixaban (N=1949)	Enoxaparin (N=1917)	P Value†
Duration of surgery — hr					0.20
Mean	1.48	1.50	1.45	1.43	
Range	0.0–6.75	0.0–8.75	0.0–6.00	0.0–5.58	
Use of tourniquet — no./total no. (%)	0/2673	1/2659 (<0.1)	0/1949	1/1917 (<0.1)	0.50
Use of cement — no./total no. (%)	734/2673 (27.5)	763/2659 (28.7)	528/1949 (27.1)	530/1917 (27.6)	0.70
Indication for surgery — no./total no. (%)					
Osteoarthritis	1529/2673 (57.2)	1536/2659 (57.8)	1129/1949 (57.9)	1094/1917 (57.1)	0.59
Degenerative joint disease	633/2673 (23.7)	630/2659 (23.7)	454/1949 (23.3)	465/1917 (24.3)	0.48
Rheumatoid arthritis	55/2673 (2.1)	45/2659 (1.7)	36/1949 (1.8)	30/1917 (1.6)	0.50
Other	739/2673 (27.6)	726/2659 (27.3)	550/1949 (28.2)	521/1917 (27.2)	0.47
Duration of hospitalization — days					0.72
Mean	9.3	9.2	9.2	9.1	
Range	1.0–82.0	1.0–62.0	2.0–45.0	1.0–62.0	
Geographic region — no. (%)					0.90
Europe	1495 (55.2)	1495 (55.4)	1084 (55.6)	1086 (56.7)	
North America	809 (29.9)	797 (29.5)	609 (31.2)	580 (30.3)	
Asia–Pacific Islands	278 (10.3)	279 (10.3)	185 (9.5)	178 (9.3)	
Latin America	126 (4.7)	128 (4.7)	71 (3.6)	73 (3.8)	
Estimated creatinine clearance >60 ml/min — no. (%)	2381 (87.9)	2376 (88.0)	1731 (88.8)	1716 (89.5)	0.48

* The primary efficacy analysis was performed on data from all patients who underwent randomization and who had a primary efficacy outcome that could be evaluated. The primary efficacy outcome was the composite of adjudicated asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the intended treatment period (i.e., from randomization to day 32 to 38 or to within 2 days after the last dose of study medication was administered, whichever was longer).

† P values are for post hoc comparisons of baseline characteristics between patients in the apixaban and enoxaparin groups who were included in the primary efficacy analysis. Two-sample t-tests were performed on the means of continuous variables. For categorical variables, chi-square tests were used for variables with at least five expected events, and Fisher's exact tests were used for those with fewer than five expected events.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Race or ethnic group was determined by the investigator.

¶ The surgery-specific characteristics were measured after the first preoperative subcutaneous injection of enoxaparin or placebo, rather than at baseline; therefore, these characteristics were assessed in the safety-analysis cohort (the cohort that received at least one dose of the study drug).

in risk, 0.1 percentage points; 95% CI, −0.3 to 0.6) (Table 3). Thirteen of the 22 major bleeding events in the apixaban group occurred before the first dose was administered; therefore, major bleeding with an onset after the first dose of apixaban occurred in 9 of 2673 patients (0.3%; 95% CI, 0.2 to 0.7). No bleeding event in either group was related to spinal or epidural anesthesia.

The composite of major and clinically relevant nonmajor bleeding occurred in 129 patients who received apixaban (4.8%) and in 134 patients who received enoxaparin (5.0%) (absolute difference in risk, −0.2 percentage points; 95% CI, −1.4 to 1.0). Of the 129 events that occurred in the apixaban group, 33 occurred before the first dose was administered. Thus, major or clinically relevant nonmajor bleeding with onset after the first dose of apixaban occurred in 96 of the 2673 patients (3.6%; 95% CI, 3.0 to 4.4). The severity and site of bleeding, as well as the frequency of bleeding

Table 2. Efficacy Outcomes.*

Outcome	Patients with Events		Relative Risk (95% CI)	Absolute Difference in Risk (95% CI)	P Value†
	Apixaban	Enoxaparin			
	no./total no. (%)			*percentage points*	
Intended treatment period					
All venous thromboembolism and death from any cause‡	27/1949 (1.4)	74/1917 (3.9)	0.36 (0.22 to 0.54)	−2.5 (−3.5 to −1.5)	<0.001
Major venous thromboembolism§	10/2199 (0.5)	25/2195 (1.1)	0.40 (0.15 to 0.80)	−0.7 (−1.3 to −0.2)	0.01
Symptomatic venous thromboembolism and death from venous thromboembolism	4/2708 (0.1)	10/2699 (0.4)	0.40 (0.01 to 1.28)	−0.2 (−0.6 to 0.06)	0.11
Symptomatic deep-vein thrombosis	1/2708 (<0.1)	5/2699 (0.2)			
Pulmonary embolism					
Nonfatal	2/2708 (<0.1)	5/2699 (0.2)			
Fatal	1/2708 (<0.1)	0/2699			
Deep-vein thrombosis					
All¶	22/1944 (1.1)	68/1911 (3.6)			
Proximal‖	7/2196 (0.3)	20/2190 (0.9)			
Death	3/2708 (0.1)	1/2699 (<0.1)			
Intended follow-up period					
Symptomatic deep-vein thrombosis	0/2598	3/2577 (0.1)			
Pulmonary embolism					
Nonfatal	0/2598	4/2577 (0.2)			
Fatal	0/2598	0/2577			
Death	2/2598 (<0.1)	1/2577 (<0.1)			

* The efficacy outcomes were as follows: all venous thromboembolism and death from any cause (the primary efficacy outcome), which comprised asymptomatic or symptomatic deep-vein thrombosis, pulmonary embolism, and death from any cause; major venous thromboembolism (the main secondary efficacy outcome), which comprised asymptomatic or symptomatic proximal deep-vein thrombosis and nonfatal or fatal pulmonary embolism; symptomatic venous thromboembolism or death related to venous thromboembolism, which comprised symptomatic deep-vein thrombosis and nonfatal or fatal pulmonary embolism; asymptomatic or symptomatic proximal deep-vein thrombosis; nonfatal or fatal pulmonary embolism; and death. The intended treatment period was the period from randomization to day 32 to 38 or to within 2 days after the last dose of study medication, whichever was longer. The intended follow-up period was the 60-day period starting after the intended treatment period ended. Data are from all patients who underwent randomization, except where noted.

† The P values are two-sided P values for a superiority test on relative risk.

‡ Data are shown for randomly assigned patients who had a bilateral venogram that could be evaluated or adjudicated symptomatic venous thromboembolism or who died from any cause.

§ Data are shown for randomly assigned patients who had an adjudicated bilateral venogram that could be evaluated for proximal deep-vein thrombosis or who had adjudicated major venous thromboembolism.

¶ Data are shown for randomly assigned patients who had an adjudicated bilateral venogram that could be evaluated or who had adjudicated symptomatic or asymptomatic deep-vein thrombosis.

‖ Data are shown for randomly assigned patients who had an adjudicated bilateral venogram that could be evaluated for proximal deep-vein thrombosis or who had adjudicated symptomatic proximal deep-vein thrombosis.

events that occurred before the first postoperative dose of the study medication, are summarized in Table 3.

Elevations in hepatic aminotransferase levels and in bilirubin levels were uncommon in both treatment groups. Both arterial thromboembolic events and thrombocytopenia during the combined treatment and follow-up period were uncommon and affected similar proportions of patients in the two groups (Table 4). The incidences of reported adverse events and serious adverse events were also similar in the two groups (see the Supplementary Appendix).

Four patients died during the intended treatment period (three in the apixaban group and one in the enoxaparin group). Three additional deaths

Table 3. Bleeding Events during the Treatment Period.*

Event	Apixaban (N=2673)	Enoxaparin (N=2659)	Absolute Risk Difference *percentage points (95% CI)*	P Value
Adjudicated major bleeding events				
No. of patients	22	18		
% (95% CI)	0.8 (0.5 to 1.3)	0.7 (0.4 to 1.1)	0.1 (–0.3 to 0.6)	0.54
Time from first dose of study drug to event — days	4.0±5.41	6.6±8.02		
Diagnostic criterion for major bleeding — no. of patients (%)				
Decrease in hemoglobin of ≥2 g/dl within 24 hours	13 (0.5)	10 (0.4)		
Transfusion of ≥2 units of packed red cells	16 (0.6)	14 (0.5)		
Bleeding at a critical site — no. of patients (%)†	0	0		
Hemarthrosis requiring reoperation or reintervention — no. of patients (%)	1 (<0.1)	1 (<0.1)		
Fatal bleeding — no. of patients (%)	0	0		
Bleeding at the surgical site — no. of patients (%)‡	18 (0.7)	16 (0.6)		
Hemarthrosis in the operated joint	2 (<0.1)	4 (0.2)		
Other bleeding at the surgical site	17 (0.6)	15 (0.6)		
Nonsurgical bleeding events — no. of patients (%)‡	5 (0.2)	2 (<0.1)		
Gastrointestinal	4 (0.1)	0		
Other non–surgical-site bleeding	5 (0.2)	2 (<0.1)		
Events that occurred before the first postoperative dose of study drug — no. of patients (%)	13 (0.5)	7 (0.3)		
Adjudicated clinically relevant nonmajor bleeding				
No. of patients	109	120		
% (95% CI)	4.1 (3.4 to 4.9)	4.5 (3.8 to 5.4)	–0.4 (–1.5 to 0.7)	0.43
Time from first dose of study drug to event — days	8.2±8.22	7.0±6.47		
Bleeding at the surgical site — no. of patients (%)‡	79 (3.0)	88 (3.3)		
Nonsurgical bleeding events — no. of patients (%)‡	32 (1.2)	36 (1.4)		
Events that occurred before the first postoperative dose of study drug — no. of patients (%)	21 (0.8)	15 (0.6)		
Adjudicated major or clinically relevant nonmajor bleeding events				
All events				
No. of patients	129	134		
% (95% CI)	4.8 (4.1 to 5.7)	5.0 (4.3 to 5.9)	–0.2 (–1.4 to 1.0)	0.72
Events that occurred before the first postoperative dose of study drug — no. of patients (%)	33 (1.2)	19 (0.7)		
Minor bleeding events — no. of patients (%)§	184 (6.9)	200 (7.5)		
All bleeding events				
No. of patients	313	334		
% (95% CI)	11.7 (10.6 to 13.0)	12.6 (11.4 to 13.9)	–0.9 (–2.6 to 0.9)	0.34

* Patients could be counted in more than one category of bleeding events.
† Bleeding at a critical site included intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding and intramuscular bleeding with the compartment syndrome.
‡ These data were based on reports by the investigators.
§ Included are patients in whom the most severe bleeding event was minor bleeding.

occurred during the intended follow-up period (two in the apixaban group and one in the enoxaparin group). Pulmonary embolism was the adjudicated cause of death in one patient, who died on day 9 of apixaban treatment. The adjudicated cause of death in all the other patients was not related to venous thromboembolism or bleeding.

DISCUSSION

In this study, apixaban, administered at a dose of 2.5 mg twice daily starting 12 to 24 hours (mean, 19) after elective hip replacement and continued for 35 days, was more effective in preventing venous thromboembolism than was standard prophylaxis with the use of enoxaparin at a dose of 40 mg per day starting the evening before surgery. The apixaban regimen significantly reduced the absolute risk of venous thromboembolism, including the clinically important measure of major venous thromboembolism. Superior efficacy was achieved without an increase in the risk of bleeding, since the proportion of patients with major or clinically relevant nonmajor bleeding was similar in the two groups (4.8% with apixaban and 5.0% with enoxaparin).

Bleeding episodes were counted from the time of the preoperative injection of enoxaparin or placebo, but the first dose of apixaban was given after surgery. Bleeding events recorded before the initiation of oral therapy cannot be attributed to apixaban and must have been due to surgery alone. Thirteen of the 22 major bleeding events in the apixaban group occurred before the first dose was administered (Table 3). Thus, after initiation of apixaban therapy, the rate of major bleeding was 0.3% (9 of 2673 patients). In the enoxaparin group, 7 of 18 major bleeding events occurred before the first postoperative dose of enoxaparin, and the rate of major bleeding after the first postoperative dose of enoxaparin was thus 0.4% (11 of 2659 patients). Although it is not possible to rule out a contribution of the preoperative enoxaparin dose to bleeding in the individual patient, systematic reviews of the literature[16,17] suggest that the timing of this dose, given 12 hours or more before surgery, is unlikely to increase the incidence of major bleeding and that bleeding episodes that occur before the first postoperative dose of enoxaparin are due predominantly to surgery.

An advantage of effective and safe, fixed-dose, oral prophylaxis is the ease of use, which makes the recommended treatment duration of 35 days after hip replacement more achievable with oral drugs than with daily injections. Starting prophylaxis after surgery could allow the more ready use of regional anesthesia, in keeping with current guidelines that address concurrent anticoagulant treatment.[18]

Several aspects of the study design and outcome measures suggest that our conclusions are valid. In studies such as ours, patients cannot be included in efficacy analyses if the quality of the venograms is suboptimal or if venography is not performed (e.g., if patients withdraw consent or if there are clinical or technical reasons for not performing the test). A total of 28.0% of the patients in the apixaban group (759 of 2708 patients) and 29.0% of the patients in the enoxaparin group (782 of 2699) could not be evaluated for the primary efficacy analyses. These proportions are unlikely to have biased the observed results. Because the patients in the two study groups who could not be evaluated had similar baseline demographic characteristics and similar reasons for not having assessable venograms (Fig. 1), it is probable that the between-group differences in the rates of venous thromboembolism would remain similar. In addition, the randomization was stratified and balanced according to study center, and treatment assignments were concealed in order to minimize ascertainment bias. Most important, the findings with respect to major venous thromboembolism are likely to be valid because two thirds of the technically suboptimal venograms had proximal segments that could be interpreted (Fig. 1). Of the patients in the apixaban and enoxaparin groups who underwent randomization, 81.2% (2199 of 2708 patients) and 81.3% (2195 of 2699), respectively, could therefore be evaluated for major venous thromboembolism. Finally, the review of event rates to determine whether the sample size was adequate for testing noninferiority of the primary efficacy outcome was prespecified, with pooled outcome rates examined and treatment assignments concealed to prevent bias.

Other new anticoagulant drugs have been compared with enoxaparin at a dose of 40 mg per day in patients undergoing elective hip replacement, and those study drugs were also administered for 35 days. Studies of two dabigatran regimens (150 mg per day and 220 mg per day), as compared with enoxaparin, showed statistically noninferior efficacy rates and similar bleeding rates.[6,7] Rivaroxaban at a dose of 10 mg per day was more

Table 4. Summary of Safety End Points with Onset during the Treatment and Follow-up Periods.*

Safety End Point	Apixaban			Enoxaparin		
	Treatment Period (N=2673)	Follow-up Period (N=2599)	Total (N=2673)	Treatment Period (N=2659)	Follow-up Period (N=2576)	Total (N=2659)
	number of patients/total number (percent)					
Levels of both aminotransferases >3×ULN on same date†	34/2629 (1.3)	3/2436 (0.1)	37/2635 (1.4)	40/2616 (1.5)	6/2396 (0.3)	46/2620 (1.8)
Total serum bilirubin >2×ULN	24/2630 (0.9)	3/2449 (0.1)	27/2635 (1.0)	12/2617 (0.5)	1/2416 (<0.1)	13/2620 (0.5)
Levels of either aminotransferase >3×ULN and bilirubin >2×ULN on same date	7/2629 (0.3)	3/2410 (0.1)	10/2635 (0.4)	3/2613 (0.1)	1/2386 (<0.1)	4/2618 (0.2)
Myocardial infarction	5/2673 (0.2)	4/2599 (0.2)	9/2673 (0.3)	3/2659 (0.1)	1/2576 (<0.1)	4/2659 (0.2)
Stroke	1/2673 (<0.1)	0/2599	1/2673 (<0.1)	4/2659 (0.2)	1/2576 (<0.1)	5/2659 (0.2)
Thrombocytopenia‡	2/2673 (0.1)	1/2599 (<0.1)	3/2673 (0.1)	3/2659 (0.1)	2/2576 (0.1)	5/2659 (0.2)

* ULN denotes the upper limit of the normal range.
† Aminotransferase levels refer to serum levels of alanine aminotransferase and aspartate aminotransferase.
‡ Thrombocytopenia was defined as a decline in the platelet count to less than 100,000 per cubic millimeter in patients with a postoperative count of more than 150,000 per cubic millimeter or more than a 50% decline if the postoperative count was 150,000 per cubic millimeter or less.

effective than enoxaparin and was associated with significantly lower incidences of total venous thromboembolism and major venous thromboembolism, whereas the rates of major bleeding and clinically relevant nonmajor bleeding were similar or marginally higher.[19]

In our earlier studies of the use of apixaban in patients undergoing elective knee replacement, apixaban at a dose of 2.5 mg twice daily was more effective than enoxaparin at a dose of 40 mg per day initiated before surgery and had a similar bleeding profile.[12] When apixaban was compared with the more intensive postoperative enoxaparin regimen of 30 mg twice daily (a 50% higher total daily dose), apixaban had similar efficacy and was associated with a significantly lower rate of major or clinically relevant nonmajor bleeding, although the efficacy results did not meet one of two prespecified statistical criteria for noninferiority.[11] The balance of benefit to risk therefore favored apixaban in both trials.

The results of our study extend this favorable balance to patients undergoing elective hip replacement. Apixaban at a dose of 2.5 mg twice daily was superior to enoxaparin at a dose of 40 mg per day, preventing one episode of major venous thromboembolism for each 147 patients treated, without adding to the risk of bleeding.

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