EDITORIAL

Therapeutic Potential of Oral Factor Xa Inhibitors

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Venous thromboembolism is the third leading cause of cardiovascular death, after myocardial infarction and stroke.[1] Total hip or knee arthroplasty is the procedure with the highest risk of venous thromboembolism.[2] In this issue of the *Journal*, two studies affirm and extend the efficacy and safety of the novel oral factor Xa inhibitors, rivaroxaban and apixaban, in the management of venous thromboembolic disease.[3,4] In the Acute DVT Study,[3] rivaroxaban (at a dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared with enoxaparin followed by warfarin or acenocoumarol, for 3, 6, or 12 months, in patients with acute, symptomatic deep-vein thrombosis. Rivaroxaban had noninferior efficacy with respect to recurrent venous thromboembolism, with similar rates of hemorrhage. The Continued Treatment Study[3] confirmed the persistent risk of recurrent venous thromboembolism after initial treatment, as shown by Ridker and colleagues,[5] and lends further support to extending the duration of anticoagulant therapy, particularly given the low rates of major bleeding with rivaroxaban (0.7%). Lassen and colleagues studied thromboprophylactic regimens in patients undergoing total hip replacement.[4] Participants were randomly assigned to apixaban, at a dose of 2.5 mg orally twice daily, or enoxaparin, at a dose of 40 mg subcutaneously every 24 hours, with the treatments initiated perioperatively and continued for 35 days after surgery. Apixaban was associated with lower rates of venous thromboembolism without an increase in bleeding complications.

The oral factor Xa inhibitors represent a major advance in the prevention and treatment of thromboembolic disease. Factor Xa is strategically positioned at the juncture of the intrinsic and extrinsic coagulation pathways proximal to thrombin. The potential impact of these oral, highly specific, fixed-dose drugs that do not require routine monitoring will no doubt be substantial. Currently, millions of people worldwide are relegated to receiving no therapy or therapy that has been proven to be ineffective, because they lack access to the monitoring expertise needed to safely and effectively administer warfarin. It is conceivable that the oral factor Xa inhibitors, as compared with warfarin, will prove to be safer in clinical practice because they are administered in fixed doses, do not interfere with diet, and have fewer interactions with other drugs. Given the nine different tablet strengths of warfarin, transitions in care settings and fluctuations in health status invariably create opportunities for unintended harm. A growing appreciation of the hazards of warfarin therapy prompted the Food and Drug Administration to issue a black-box warning for warfarin in October 2006.[6] The factor Xa inhibitors that are most advanced in clinical development are rivaroxaban, apixaban, and edoxaban. (Other factor Xa inhibitors in development include betrixaban, YM150, and TAK-442.) Unlike the case with warfarin, drug elimination in the case of the factor Xa inhibitors involves multiple pathways. The degree of renal clearance is 66% in the case of rivaroxaban, 25% in the case of apixaban, and 35% in the case of edoxaban. As compared with warfarin's half-life of 20 to 60 hours, the respective half-lives of these agents are 7 to 11 hours, 12 hours, and 9 to 11 hours. As shown in the study by the EINSTEIN investigators, the rapid onset of action obviates the need for heparin in the acute management of venous thrombosis. The rapid onset of action also has impli-

cations for the appropriate timing of the initiation of the drug after the procedure, given the need for wound hemostasis. The shorter half-life of these agents may improve their overall safety profile but, conversely, will also result in the drugs' providing less protection if doses are missed. All these drugs are metabolized to different degrees by cytochrome P-450 3A4 (CYP3A4) and are substrates for P-glycoprotein. Therefore, the concomitant use of drugs that inhibit both pathways, such as azole antifungal agents or protease inhibitors, is contraindicated.[7]

Each of the factor Xa inhibitors is being evaluated in at least one large-scale phase 3 trial of stroke prevention in patients with atrial fibrillation. Positive results from the completed Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF; ClinicalTrials.gov number, NCT00403767) were recently presented at the annual scientific sessions of the American Heart Association.[8] The randomized trial of Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES, NCT00496769) was stopped early because the efficacy of apixaban had been shown.[9] The results of ongoing trials involving patients with atrial fibrillation, in which warfarin is the active comparator, are expected in 2011: the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation study (ARISTOTLE, NCT00412984), in which apixaban is being tested with a dose of 5 mg twice daily, and the Global Study to Assess the Safety and Effectiveness of DU-176b versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48, NCT00781391), in which two doses of edoxaban, 30 mg and 60 mg, each administered once daily, are being compared with warfarin.

Translating the efficacy and safety that have been shown in clinical trials to real-world practice is often a challenge because, as compared with patients in real-world practices, participants in trials are usually younger, have less medically complex illnesses, are more likely to be adherent, and have been specifically selected on the basis of having a lower risk of bleeding. Concomitant antiplatelet therapy is either discouraged or considered to be an exclusion criterion. The mean age of participants undergoing hip arthroplasty in the study by Lassen et al. was 60 years, and approximately 89% of the participants had normal renal function. Similarly, the mean age of participants with acute symptomatic deep-vein thrombosis in the study by the EINSTEIN investigators was 56 years, and 92% had a creatinine clearance of 50 ml per minute or more. Because both the risk of thrombosis and the risk of hemorrhage increase substantially with age and with burden of chronic disease, the effectiveness of the novel agents in real-world practice will need to be closely monitored, particularly among older adults with renal impairment. The critical role of baseline risk and the additive hazards of combination antiplatelet therapy and bleeding were highlighted by the recent early termination, because of increased bleeding with apixaban, of the Apixaban for Prevention of Acute Ischemic Events 2 trial (APPRAISE-2, NCT00831441), in which patients with a recent acute coronary syndrome who were receiving single or dual antiplatelet therapy were randomly assigned to apixaban or placebo.[10]

Alternatives to warfarin have been long awaited. The oral factor Xa inhibitors show great promise. The reversibility of the drugs' effects and the ability to measure the anticoagulant effect in specific situations will continue to be highly desirable features and will help to allay physicians' concerns. If these novel, breakthrough, oral anticoagulant drugs prove to be effective across the broad spectrum of patients in routine care and are conscientiously priced, the worldwide impact will be huge.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Apixaban versus Enoxaparin for Thromboprophylaxis after Hip Replacement

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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.)

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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

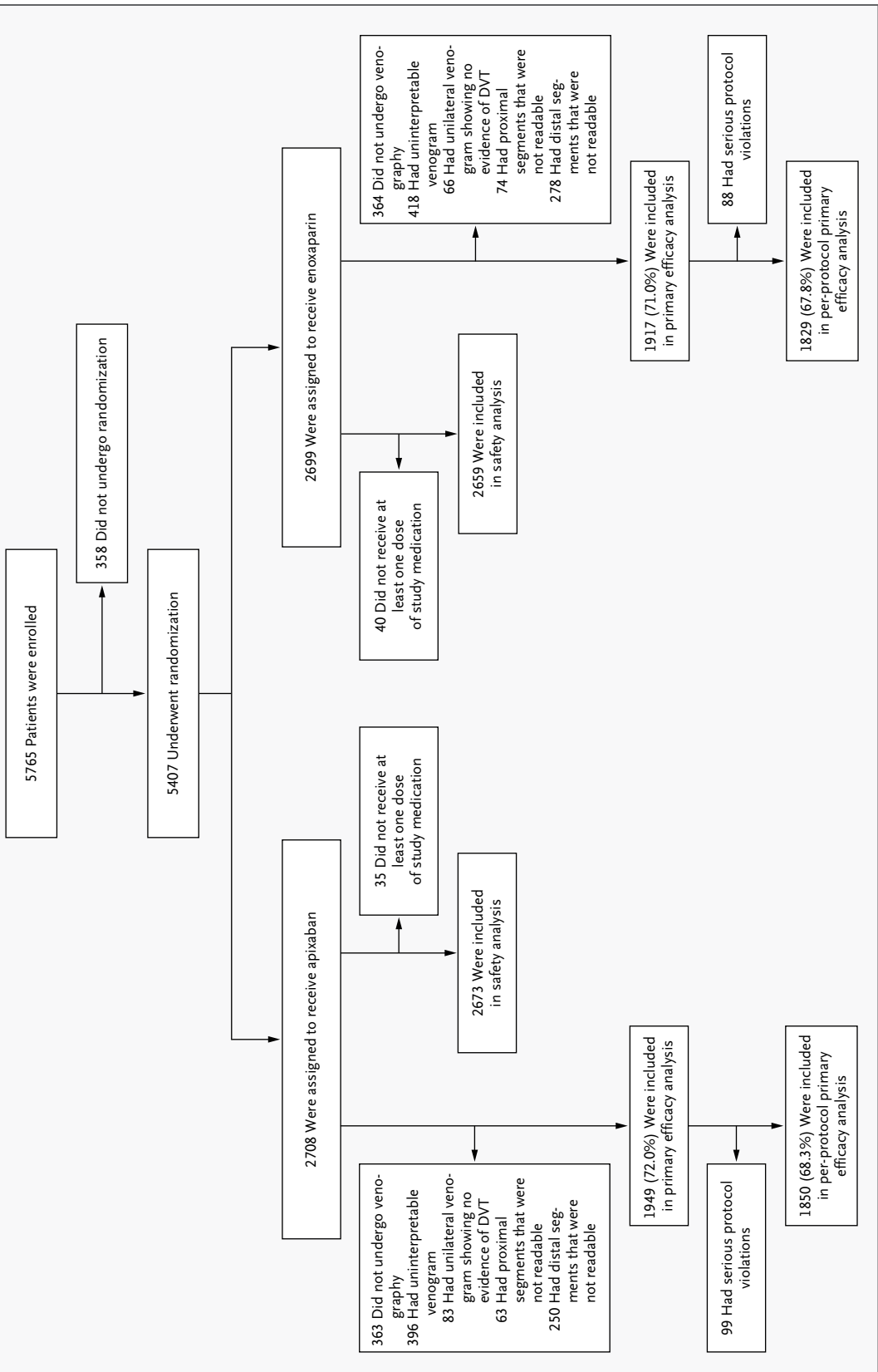

Figure 1. Enrollment and Randomization.

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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

ABSTRACT

BACKGROUND

Rivaroxaban, an oral factor Xa inhibitor, may provide a simple, fixed-dose regimen for treating acute deep-vein thrombosis (DVT) and for continued treatment, without the need for laboratory monitoring.

METHODS

We conducted an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT. In parallel, we carried out a double-blind, randomized, event-driven superiority study that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism. The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding in the initial-treatment study and major bleeding in the continued-treatment study.

RESULTS

The study of rivaroxaban for acute DVT included 3449 patients: 1731 given rivaroxaban and 1718 given enoxaparin plus a vitamin K antagonist. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%], vs. 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001). The principal safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%], vs. 42 with placebo [7.1%]; hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (P=0.11).

CONCLUSIONS

Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation. (Funded by Bayer Schering Pharma and Ortho-McNeil; ClinicalTrials.gov numbers, NCT00440193 and NCT00439725.)

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*The investigators participating in the EINSTEIN–DVT and EINSTEIN–Extension Studies are listed in the Supplementary Appendix, available at NEJM.org.

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Acute venous thromboembolism (i.e., deep-vein thrombosis [DVT] or pulmonary embolism) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1000 persons in the general population.[1,2] Short-term treatment is effective, with the risk of recurrent disease — the major complication — reduced from an estimated 25% to about 3% during the first 6 to 12 months of therapy.[3] The risk of recurrence remains after treatment ends and can reach 5 to 10% during the first year.[4,5]

Standard treatment for acute venous thromboembolism is limited by the need for parenteral heparin initially, with overlapping administration of a vitamin K antagonist. This presents a challenge to outpatient management,[6] since treatment with a vitamin K antagonist requires laboratory monitoring and dose adjustment and may be complicated by drug and food interactions. After the first year, the annual risk of major bleeding associated with vitamin K antagonists is 1 to 2%.[6] Consequently, the balance between the risks and the benefits of continued therapy remains a subject of debate, despite the high long-term risk of recurrent venous thromboembolism. A simple solution to some of these issues could be administration of an oral anticoagulant that does not require laboratory monitoring yet is effective as a single agent for the treatment of acute venous thromboembolism and for continued treatment.

Rivaroxaban, an orally active, direct factor Xa inhibitor, is effective in the prevention of venous thromboembolism after orthopedic surgery. It does not require laboratory monitoring and has no food interactions and only a few drug interactions.[7-9]

In two dose-finding studies, we established the feasibility of single-agent therapy with rivaroxaban in patients with DVT.[10,11] This led to the EINSTEIN program, consisting of three randomized trials of rivaroxaban: one for the treatment of acute deep-vein thrombosis (the Acute DVT Study), one for the treatment of acute pulmonary embolism (the Acute PE Study), and one for continued treatment in patients who have received treatment for acute deep-vein thrombosis or pulmonary embolism (the Continued Treatment Study). We report the results of the first and third trials; the second trial is ongoing.

METHODS

STUDY DESIGN AND OVERSIGHT

The Acute DVT Study was a randomized, open-label study that compared the efficacy and safety of rivaroxaban with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients with acute, symptomatic DVT. The Continued Treatment Study (EINSTEIN–Extension) was a double-blind study in which patients with confirmed symptomatic DVT or pulmonary embolism who had been treated for 6 or 12 months with a vitamin K antagonist or rivaroxaban were randomly assigned to receive continued treatment with rivaroxaban or placebo. Both trials were sponsored by Bayer Schering Pharma and Ortho-McNeil. The trials were conducted in accordance with the protocol (available with the full text of this article at NEJM.org).

The steering committee had final responsibility for the study designs, clinical protocols, study oversight, and verification and analyses of the data. The protocols were approved by the institutional review board at each center, and written informed consent was obtained from all patients. The data were collected and maintained by the sponsor. All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignments. An independent data and safety monitoring board periodically reviewed outcomes. The writing committee wrote the manuscript and vouches for the accuracy and completeness of the reported data and analyses and the fidelity of the study to the protocol.

PATIENTS

For the Acute DVT Study, patients were eligible if they were of legal age for consent and had acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism. Patients were ineligible if they had received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours or if they had received more than a single dose of a vitamin K antagonist before randomization; if they had been treated with thrombectomy, a vena cava filter, or a fibrinolytic agent for the current episode of thrombosis; or if

they had any contraindication listed in the labeling of enoxaparin, warfarin, or acenocoumarol.

For the Continued Treatment Study, patients were eligible if they had objectively confirmed, symptomatic DVT or pulmonary embolism and had been treated for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or from routine care) or rivaroxaban (in the EINSTEIN studies) and if there was equipoise with respect to the need for continued anticoagulation.

Exclusion criteria for both studies were another indication for a vitamin K antagonist; a creatinine clearance below 30 ml per minute; clinically significant liver disease (e.g., acute hepatitis, chronic active hepatitis, or cirrhosis) or an alanine aminotransferase level that was three times the upper limit of the normal range or higher; bacterial endocarditis; active bleeding or a high risk of bleeding, contraindicating anticoagulant treatment; systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breast-feeding; concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g., human immunodeficiency virus protease inhibitors or systemic ketoconazole) or inducers (e.g., rifampicin, carbamazepine, or phenytoin); participation in another experimental pharmacotherapeutic program within 30 days before screening; and a life expectancy of less than 3 months.

In both studies, patients were randomly assigned to a study group with the use of a computerized voice–response system, with stratification by country. The intended treatment duration was determined by the treating physician.

TREATMENT REGIMENS

In the Acute DVT Study, patients assigned to receive oral rivaroxaban were given 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily for the intended 3, 6, or 12 months of treatment. Patients who were assigned to standard therapy received subcutaneous enoxaparin, 1.0 mg per kilogram of body weight twice daily, and either warfarin or acenocoumarol, started within 48 hours after randomization. Enoxaparin was discontinued when the international normalized ratio (INR) was 2.0 or more for 2 consecutive days and the patient had received at least 5 days of enoxaparin treatment. The dose of the vitamin K antagonist was adjusted to maintain an INR of 2.0 to 3.0. The INR was determined at least once per month. The time during which the INR was within the therapeutic range was calculated for each patient from the discontinuation of heparin until the end of treatment, including interruptions. For the Continued Treatment Study, patients were assigned to either rivaroxaban, 20 mg once daily, or matching placebo for the intended treatment duration of 6 or 12 months.

In both studies, the use of nonsteroidal antiinflammatory drugs and antiplatelet agents was discouraged. If indicated, aspirin (up to 100 mg per day), clopidogrel (75 mg per day), or both were allowed.

SURVEILLANCE AND FOLLOW-UP

In both studies, patients were followed for the intended treatment duration and seen at fixed intervals that were identical for the rivaroxaban and comparison groups, at which time a checklist was used to elicit information on symptoms and signs of recurrent venous thromboembolism, bleeding, and adverse events. Patients were instructed to report to the study center immediately if any of these events occurred. In cases of suspected venous thromboembolism, the protocol required objective testing.

OUTCOME ASSESSMENTS

For both studies, the primary efficacy outcome was symptomatic, recurrent venous thromboembolism, defined as the composite of DVT or nonfatal or fatal pulmonary embolism, with the use of diagnostic criteria described previously[12] (see the Supplementary Appendix, available at NEJM .org). Death was classified as due to pulmonary embolism, bleeding, or other established causes. Pulmonary embolism was considered the cause of death if there was objective documentation or if death could not be attributed to a documented cause and pulmonary embolism could not be confidently ruled out.

For the Acute DVT Study, the principal safety outcome was clinically relevant bleeding, defined as the composite of major or clinically relevant nonmajor bleeding. For the Continued Treatment Study, the principal safety outcome was major bleeding. Criteria for bleeding were described previously[12] (see the Supplementary Appendix).

Predefined secondary outcomes included all-cause mortality, vascular events (acute coronary syndrome, ischemic stroke, transient ischemic at-

tack, or systemic embolism), and net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding). In addition, analyses of the treatment effects and bleeding were performed in prespecified subgroups in both studies.[13]

STATISTICAL ANALYSIS

The Acute DVT Study was designed as an event-driven, noninferiority study. Assuming equal efficacy in the two study groups, a total of 88 events would provide a power of 90% to demonstrate that rivaroxaban is noninferior to standard therapy, with the use of a margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio at a two-sided alpha level of 0.05. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy. On the basis of a 3% incidence of the primary efficacy outcome, we calculated that we would need a sample of approximately 3000 patients. However, it was specified a priori that the steering committee would decide to stop enrollment when it was estimated that 88 events would be reached. This decision was to be made without knowledge of the outcomes in the treatment groups. When enrollment was discontinued, patients completed their assigned treatment, except for patients in the 12-month stratum who had completed at least 6 months of treatment.

The Continued Treatment Study was an event-driven, superiority study. Assuming a 70% relative risk reduction with rivaroxaban, a total of 30 events would provide a power of 90% to demonstrate that rivaroxaban is superior to placebo at a two-sided alpha level of 0.05. On the basis of a frequency of the primary outcome of 3.5% for the placebo group, we calculated that we would need a sample of approximately 1300 patients. However, the final sample size was determined as described for the Acute DVT Study, with a minimum treatment duration of 3 months.

For both studies, the primary efficacy analysis was performed on an intention-to-treat basis with the use of a stratified intended-duration Cox proportional-hazards model, adjusted for the presence of a malignant condition at baseline in the Acute DVT Study and pretreatment in the Continued Treatment Study. The safety analyses included all patients who received the assigned study drug. Bleeding events were included in the analyses if they occurred during treatment or within 2 days after discontinuation of the study drug.

RESULTS

STUDY PATIENTS

From March 2007 through September 2009, a total of 3449 patients underwent randomization in the Acute DVT Study (Fig. 1A). From February 2007 through March 2009, a total of 1197 patients were enrolled in the Continued Treatment Study. Of these patients, 34.1% had completed the Acute DVT Study and 19.1% had completed the Acute PE (Pulmonary Embolism) Study of the EINSTEIN program; the remaining 560 patients (47.5%) were referred from outside both these studies (Fig. 1B). Baseline characteristics of the patients for both the Acute DVT Study and the Continued Treatment Study are shown in Table 1.

TREATMENT AND FOLLOW-UP

For the Acute DVT Study, data on treatment with rivaroxaban or with enoxaparin combined with a vitamin K antagonist (standard therapy), as well as the main reasons for premature discontinuation of treatment, are shown in Table 2. In the standard-therapy group, the median duration of enoxaparin treatment was 8 days (interquartile range, 6 to 11), and the INR at the end of enoxaparin treatment was 2.0 or higher in 80.8% of patients. Overall, the INR was in the therapeutic range (2.0 to 3.0) for 57.7% of the time, above 3.0 for 16.2% of the time, and below 2.0 for 24.4% of the time. The percentage of time within the therapeutic range varied from 54.1% (month 1) to 66.4% (month 10). Because termination of the study was event-driven, the duration of treatment was shorter than intended for 102 patients (5.9%) in the rivaroxaban group and for 94 patients (5.5%) in the standard-therapy group. In the rivaroxaban group, 15 patients (0.9%) were lost to follow-up as compared with 18 patients (1.0%) in the standard-therapy group.

For the Continued Treatment Study, data on treatment with either rivaroxaban or placebo and the reasons for premature discontinuation of treatment are shown in Table 2. As a result of event-driven termination, the duration of treatment was shorter than intended for 156 patients (25.9%) in the rivaroxaban group and for 148 patients (24.9%) in the placebo group. Follow-up for the primary

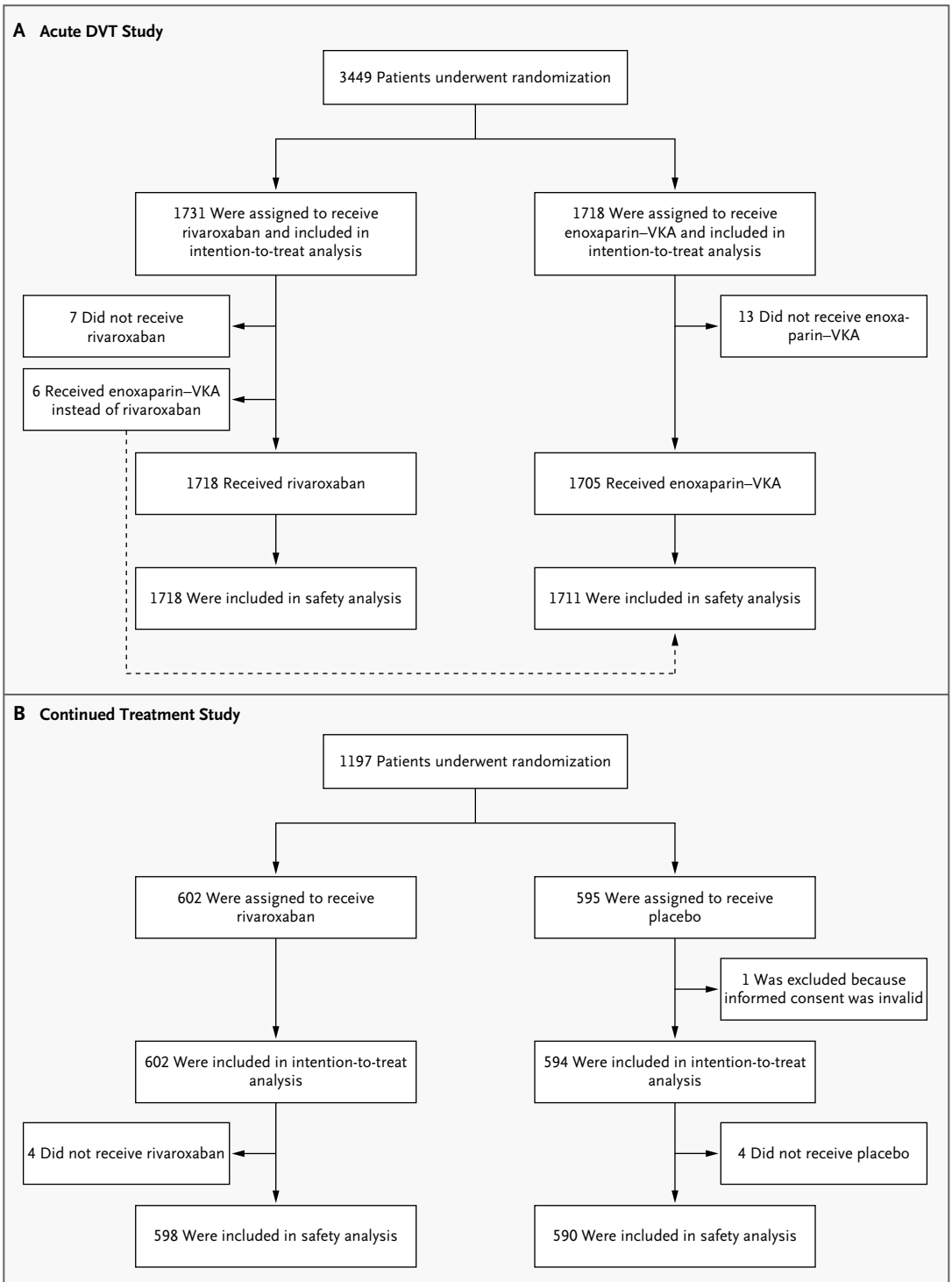

Figure 1. Numbers of Patients Who Underwent Randomization, Received the Study Drugs, and Were Included in the Efficacy and Safety Analyses in the Acute DVT and Continued Treatment Studies.

ITT denotes intention to treat, and VKA vitamin K antagonist.

Table 1. Demographic and Clinical Characteristics of Patients with Deep-Vein Thrombosis, According to the Study and the Assigned Group.*

Characteristic	Acute DVT Study		Continued Treatment Study	
	Rivaroxaban (N=1731)	Standard Therapy† (N=1718)	Rivaroxaban (N=602)	Placebo (N=594)
Age — yr	55.8±16.4	56.4±16.3	58.2±15.6	58.4±16
Male sex — no. (%)	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)
Weight — no. (%)				
≤50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)
>50–100 kg	1443 (83.4)‡	1422 (82.8)‡	491 (81.6)‡	488 (82.2)‡
>100 kg	245 (14.2)‡	246 (14.3)‡	85 (14.1)‡	87 (14.6)‡
Missing data	6 (0.3)	1 (<0.1)	16 (2.7)	14 (2.4)
Creatinine clearance — no. (%)				
<30 ml/min	6 (0.3)	9 (0.5)	0	5 (0.8)
30–49 ml/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)
50–79 ml/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)
≥80 ml/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)
Missing data	24 (1.4)	20 (1.2)	58 (9.6)	50 (8.4)
Initial diagnosis — no.				
DVT	1708	1697 (only 1 distal)	386	356
PE	12	11	216	238
Time from onset of symptoms to randomization — days				
Median	5	5	204	206
Interquartile range	3–10	3–10	188–302	189–307
Cause of DVT or PE — no. (%)				
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441(74.2)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)
Immobilization	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0
Known thrombophilic condition — no. (%)	107 (6.2)	116 (6.8)	49 (8.1)	48 (8.1)
Previous VTE — no. (%)	336 (19.4)	330 (19.2)	108 (17.9)	84 (14.1)

* Plus–minus values are means ±SD. DVT denotes deep-vein thrombosis, PE pulmonary embolism, and VTE venous thromboembolism.
† Standard therapy consisted of enoxaparin and a vitamin K antagonist.
‡ Some percentages may not total 100 because of rounding.

efficacy outcome was complete for 601 patients (99.8%) in the rivaroxaban group and for 593 patients (99.8%) in the placebo group.

CLINICAL OUTCOMES IN THE ACUTE DVT STUDY

The clinical outcomes are shown in Table 3. The primary efficacy outcome was suspected in 230 patients in the rivaroxaban group and in 215 patients in the standard-therapy group and was confirmed in 36 and 51 of these patients, respectively. Hence, the primary efficacy outcome occurred in 2.1% of patients in the rivaroxaban group and in 3.0% of patients in the standard-therapy group (hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001 for noninferiority with a one-sided test, and P=0.08 for superiority with a two-sided test). The time course of recurrent venous thromboembolism in the two treatment groups is shown in

Table 2. Characteristics of Treatment in Each Study.*

Characteristic	Acute DVT Study			Continued Treatment Study		
	Rivaroxaban (N=1731)	Enoxaparin–VKA Therapy (N=1718)	P Value	Rivaroxaban (N=602)	Placebo (N=594)	P Value
Intended duration of treatment — no. (%)			0.96			0.92
3 mo	208 (12.0)	203 (11.8)		NA	NA	
6 mo	1083 (62.6)	1083 (63.0)		360 (59.8)	357 (60.1)	
12 mo	440 (25.4)	432 (25.1)		242 (40.2)	237 (39.9)	
Pretreatment with LMWH, heparin, or fondaparinux — no. (%)	1264 (73.0)	1213 (71.0)	0.11	NA	NA	
Duration of pretreatment — no. (%)			0.14	NA	NA	
1 day	1192 (68.9)	1139 (66.3)				
2 days	68 (3.9)	67 (3.9)				
>2 days	4 (0.2)	7 (0.4)				
Pretreatment with VKA for 6–12 mo — no. (%)	NA	NA		429 (71.3)	434 (73.1)	0.49
Pretreatment with rivaroxaban for 6–12 mo — no. (%)†	NA	NA		173 (28.7)	160 (26.9)	
At least 1 dose of assigned treatment received — no. (%)	1718 (99.2)‡	1705 (99.2)	0.99	598 (99.3)	590 (99.3)	0.99
Duration of treatment with study drug — days						
3-month period			0.30	NA	NA	NA
Median	93	93				
Interquartile range	91–96	91–96				
6-month period			0.11			0.51
Median	182	181		181		
Interquartile range	179–184	178–183		177–183		
12-month period			0.36			0.81
Median	354	353		264	265	
Interquartile range	269–358	266–357		166–354	123–354	
Premature discontinuation of treatment — no. (%)	196 (11.3)	244 (14.2)	0.010	76 (12.6)	93 (15.7)	0.13
Adverse events	74 (4.3)	67 (3.9)		39 (6.5)	18 (3.0)	
Consent withdrawn	34 (2.0)	67 (3.9)		22 (3.7)	19 (3.2)	
Lost to follow-up	15 (0.9)	18 (1.0)		1 (0.2)	1 (0.2)	

* LMWH denotes low-molecular-weight heparin, NA not applicable, and VKA vitamin K antagonist.
† Two patients in each group received rivaroxaban followed by a vitamin K antagonist.
‡ Seven patients took no medication, and six patients received standard therapy (enoxaparin and a VKA) instead of rivaroxaban.

Figure 2A. By day 21 (the end of twice-daily rivaroxaban dosing), the primary efficacy outcome had occurred in 21 patients (1.2%) in the rivaroxaban group and in 29 patients (1.7%) in the standard-therapy group. The results of the on-treatment and per-protocol analyses were similar to those of the intention-to-treat analysis (data not shown).

The principal safety outcome — first major or clinically relevant nonmajor bleeding — occurred in 139 patients (8.1%) given rivaroxaban and in 138 patients (8.1%) given standard therapy (hazard ratio with rivaroxaban, 0.97; 95% CI, 0.76 to 1.22; P=0.77). The time course for the principal safety outcome is shown in Figure 3.

The outcome of a net clinical benefit occurred in 51 (2.9%) of the patients who received rivaroxaban and in 73 (4.2%) of the patients who received standard therapy (hazard ratio, 0.67; 95% CI, 0.47 to 0.95; P=0.03). The relative efficacy and safety were consistent across the prespecified subgroups (Fig. 1 and 2 in the Supplementary Appendix). Vascular events during study treatment occurred

Table 3. Clinical Outcomes in the Acute DVT Study.*

Outcome	Rivaroxaban	Enoxaparin–VKA	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	1731	1718		
Recurrent VTE	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001†
Type of recurrent VTE				
Fatal PE	1	0		
PE could not be ruled out	3	6		
Nonfatal PE	20	18		
Recurrent DVT plus PE	1	0		
Recurrent DVT	14	28		
Net clinical benefit in terms of VTE plus major bleeding	51 (2.9)	73 (4.2)	0.67 (0.47–0.95)	0.03
Safety				
Safety population	1718	1711		
First major or clinically relevant nonmajor bleeding occurring during treatment	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21
Contributing to death	1 (<0.1)	5 (0.3)		
In a critical site	3 (0.2)	3 (0.2)		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	10 (0.6)	12 (0.7)		
Clinically relevant nonmajor bleeding	126 (7.3)	119 (7.0)		
Total deaths through end of intended treatment period	38 (2.2)	49 (2.9)	0.67 (0.44–1.02)	0.06
Cause of death				
PE, or PE not ruled out	4	6		
Bleeding	2‡	5		
Cancer	25	20		
Cardiovascular disease	2	4		
Other	6	14		
Adverse events				
Any event emerging during treatment	1078 (62.7)	1080 (63.1)		
Any serious event emerging during treatment	201 (12.0)	233 (13.6)		
Any event resulting in permanent discontinuation of study drug	85 (4.9)	81 (4.7)		
Any event leading to or prolonging hospitalization	193 (11.2)	211 (12.3)		

* Hazard ratios are for rivaroxaban as compared with standard therapy. CI denotes confidence interval, DVT deep-vein thrombosis, PE pulmonary embolism, VKA vitamin K antagonist, and VTE venous thromboembolism. Incidences are presented as crude values.
† The noninferiority margin was 2.0.
‡ One patient died from bleeding while not taking the study treatment.

in 12 patients (0.7%) in the rivaroxaban group and 14 patients (0.8%) in the standard-therapy group (Table 1 in the Supplementary Appendix). The combination of an alanine aminotransferase level exceeding three times the upper limit of the normal range and a bilirubin level exceeding twice the upper limit of the normal range was observed in 2 patients (0.1%) in the rivaroxaban group and 4 patients (0.2%) in the standard-therapy group (Table 2 in the Supplementary Appendix).

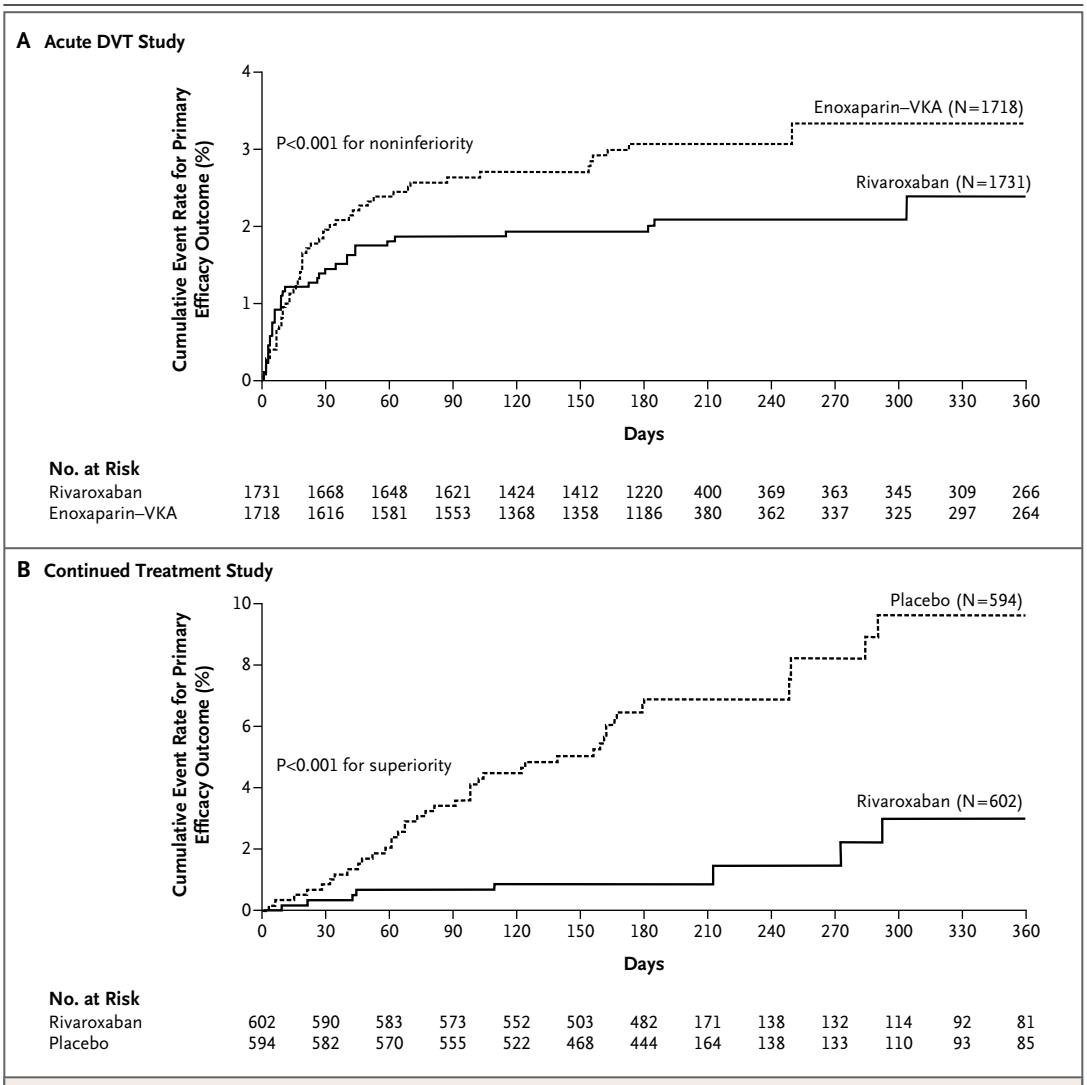

Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.
VKA denotes vitamin K antagonist.

CLINICAL OUTCOMES IN THE CONTINUED TREATMENT STUDY

The clinical outcomes are shown in Table 4. The primary efficacy outcome occurred in 8 patients (1.3%) in the rivaroxaban group as compared with 42 patients (7.1%) in the placebo group (hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001, relative risk reduction, 82%). The time course for recurrent venous thromboembolism in the two groups is shown in Figure 2B. The principal safety outcome of major bleeding occurred in 4 patients (0.7%) in the rivaroxaban group and in none of the patients in the placebo group (P=0.11).

The outcome of a net clinical benefit occurred in 12 patients (2.0%) receiving rivaroxaban and in 42 patients (7.1%) receiving placebo (hazard ratio, 0.28; 95% CI, 0.15 to 0.53; P<0.001). The relative efficacy and safety were consistent across the prespecified subgroups (Fig. 3 and 4 in the Supplementary Appendix). Vascular events occurred in 3 patients in the rivaroxaban group and 4 patients in the placebo group (Table 3 in the Supplementary Appendix). No patient in either group had the combination of an alanine aminotransferase level exceeding three times the upper limit of the normal range and a bilirubin level exceeding twice the upper limit of the normal range (Table 4 in the Supplementary Appendix).

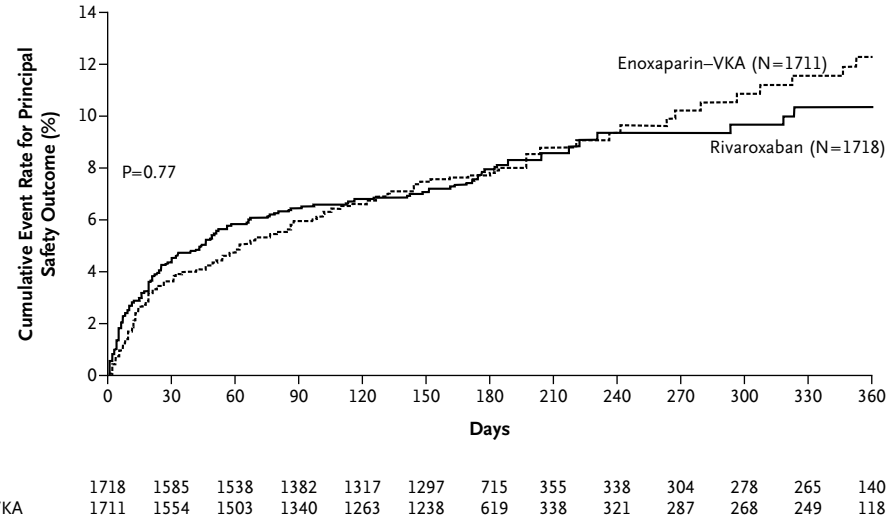

Figure 3. Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome in the Acute DVT Study.
VKA denotes vitamin K antagonist.

DISCUSSION

Our studies show that rivaroxaban alone is as effective as standard therapy, with similar safety, for the treatment of acute DVT and that when treatment is continued, rivaroxaban is very effective in preventing recurrences, as compared with placebo, and has an acceptable risk of bleeding. A unique aspect of the Acute DVT Study is the use of rivaroxaban as a single agent, replacing both low-molecular-weight heparin and a vitamin K antagonist in the treatment of DVT. Accordingly, the great majority of patients in the rivaroxaban group either did not receive low-molecular-weight heparin or received a single dose. Nevertheless, efficacy during the first weeks of treatment was similar in the two study groups. A prespecified indicator of net clinical benefit (symptomatic recurrent venous thromboembolism plus major bleeding) favored rivaroxaban. Therefore, the rivaroxaban regimen may further facilitate the outpatient management of DVT.

The purpose of the Continued Treatment Study was to explore the benefit-to-risk ratio when treatment with rivaroxaban is administered after 6 to 12 months of anticoagulation. At this time point, clinicians must often balance the long-term risks of recurrent venous thromboembolism if anticoagulation is stopped against the burden and risks of ongoing therapy.[6] Rivaroxaban reduced the rate of recurrence by 82% (from 7.1 to 1.3 clinical events), regardless of the type of index event, with a small risk of major hemorrhage (0.7%, with no fatal hemorrhages). Thus, 34 recurrent events were prevented, at the cost of 4 major bleeding events. However, the incidence of clinically relevant nonmajor bleeding was increased from 1.2% in the placebo group to 5.4% with rivaroxaban. These bleeding events were predominantly mucosal, and most patients (81%) resumed or continued the study therapy. Overall, this suggests an acceptable benefit-to-risk profile.

We performed several subgroup analyses. The results for the primary efficacy and safety outcomes were consistent and did not suggest a need for dose modification, regardless of age, sex, weight, and renal function. Furthermore, several important results of both studies warrant attention. Given earlier experience,[14] liver function was carefully monitored, and there was no suggestion of toxicity. In addition, total mortality and rates of cardiovascular events other than venous thromboembolism were low and did not differ significantly between the two groups.

Some methodologic aspects and possible limitations of the studies require comment. First, the Acute DVT Study had an open design and therefore a potential for a diagnostic-suspicion bias; however, the absolute number of patients with a suspected recurrence was slightly higher in the rivaroxaban group, whereas the proportion of patients with recurrences confirmed by the adjudica-

Table 4. Clinical Outcomes in the Continued Treatment Study.*

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	602	594		
Recurrent VTE	8 (1.3)	42 (7.1)†	0.18 (0.09–0.39)	<0.001
Type of recurrent VTE				
Fatal PE	0	1		
PE cannot be ruled out	1	0		
Nonfatal PE	2	13		
Recurrent DVT	5	31		
Safety				
Safety population	598	590		
First major or clinically relevant nonmajor bleeding	36 (6.0)	7 (1.2)	5.19 (2.3–11.7)	<0.001
Major bleeding†	4 (0.7)‡	0	NA	0.11
Contributing to death	0	0		
In a critical site	0	0		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	4	0		
Clinically relevant nonmajor bleeding†	32 (5.4)‡	7 (1.2)		
Hematuria	9	0		
Epistaxis	8	1		
Rectal	7	2		
Skin	4	2		
Uterine	3	2		
Gastrointestinal	1	0		
Related to tooth extraction	1	0		
Ear	1	0		
Total deaths	1 (0.2)	2 (0.3)		
PE, or PE not ruled out	1	1		
Bleeding	0	0		
Cancer	0	1		
Cardiovascular disease	0	0		
Other	0	0		

* Hazard ratios are for rivaroxaban as compared with placebo. CI denotes confidence interval, DVT deep-vein thrombosis, PE pulmonary embolism, and VTE venous thromboembolism.
† Some patients had more than 1 event.
‡ All 4 patients with major bleeding (gastrointestinal in 3 and menorrhagic in 1) and 6 of the 32 patients with clinically relevant nonmajor bleeding discontinued treatment permanently.

tion committee was lower (16%, vs. 25% in the standard-therapy group). This suggests that the open design did not influence the results. Second, it is important that therapy in the comparison group in the Acute DVT Study was administered to a high standard; this is indicated by the good quality of both initial low-molecular-weight heparin therapy and the switch to a vitamin K antagonist and the overall 58% of time in the therapeutic range with vitamin K antagonists, which is similar to the results of other recent thrombosis studies.[12,15] Third, the internal validity of both studies is reinforced by the low rate of loss to follow-up. Fourth, patient selection bias is unlikely:

in the Acute DVT Study, the control group had a recurrence rate of 3%, which is consistent with the rates in recent studies,[12,15] as is the 7.1% recurrence rate with placebo.[16,17] Fifth, the characteristics of the patients in each study were similar to those in other studies, which supports the generalizability of our findings.[12,15-17] Sixth, the use of placebo in the Continued Treatment Study could be criticized; however, the entry criteria specified that there should be clinical equipoise regarding the cessation or continuation of anticoagulant therapy, and patients had completed 6 to 12 months of treatment. Finally, the proportion of patients with active cancer at the time of enrollment in the Acute DVT Study was moderate (7% in both groups). Although both the relative efficacy and safety of rivaroxaban were similar to those of standard therapy in these patients, more data are needed for this subgroup.

In conclusion, oral rivaroxaban, at a dose of 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily thereafter, without the need for laboratory monitoring, may provide an effective, safe, single-drug approach to the initial and continued treatment of venous thrombosis.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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