ORIGINAL ARTICLE

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

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ABSTRACT

BACKGROUND

Apixaban, an oral factor Xa inhibitor administered in fixed doses, may simplify the treatment of venous thromboembolism.

METHODS

In this randomized, double-blind study, we compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism. The primary efficacy outcome was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding.

RESULTS

The primary efficacy outcome occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; difference in risk [apixaban minus conventional therapy], −0.4 percentage points; 95% CI, −1.3 to 0.4). Apixaban was noninferior to conventional therapy ($P<0.001$) for predefined upper limits of the 95% confidence intervals for both relative risk (<1.80) and difference in risk (<3.5 percentage points). Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received conventional therapy (relative risk, 0.31; 95% CI, 0.17 to 0.55; $P<0.001$ for superiority). The composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; $P<0.001$). Rates of other adverse events were similar in the two groups.

CONCLUSIONS

A fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding (Funded by Pfizer and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00643201).

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ENOUS THROMBOEMBOLISM, WITH AN annual incidence of 1 to 2 cases per 1000 persons in the general population, is the third most common cause of vascular death after myocardial infarction and stroke.[1] Conventional treatment consists of a parenteral anticoagulant, such as enoxaparin, for at least 5 days, and warfarin begun during this time and continued for at least 3 months.[2] Although effective, this regimen presents a challenge because enoxaparin requires daily subcutaneous injections, and warfarin therapy requires coagulation monitoring and dose adjustment.

Apixaban is an oral factor Xa inhibitor with a rapid onset of action and predictable pharmacokinetics that allow a fixed-dose regimen. With these characteristics, apixaban may simplify the treatment of venous thromboembolism by eliminating the need for initial parenteral anticoagulant therapy and laboratory monitoring, a concept supported by recent studies.[3,4] Apixaban has been shown to be effective for the prevention of recurrent venous thromboembolism in patients who have completed 6 to 12 months of anticoagulant therapy for acute venous thromboembolism, with rates of major bleeding that are similar to those for placebo.[5] In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, we compared apixaban with conventional anticoagulant therapy in patients with acute symptomatic venous thromboembolism.

METHODS

STUDY DESIGN AND OVERSIGHT

In this randomized, double-blind trial, we compared the efficacy and safety of apixaban with the efficacy and safety of conventional therapy (enoxaparin and warfarin) in patients with deep-vein thrombosis, pulmonary embolism, or both. The trial was sponsored by Bristol-Myers Squibb and Pfizer. The steering committee, consisting of academic authors and authors who were employees of Pfizer, had final responsibility for the study design, oversight, and data verification and analyses. The protocol was approved by the institutional review board at each participating center, and written informed consent was obtained from all patients. The sponsors collected and maintained the data; the academic authors had fu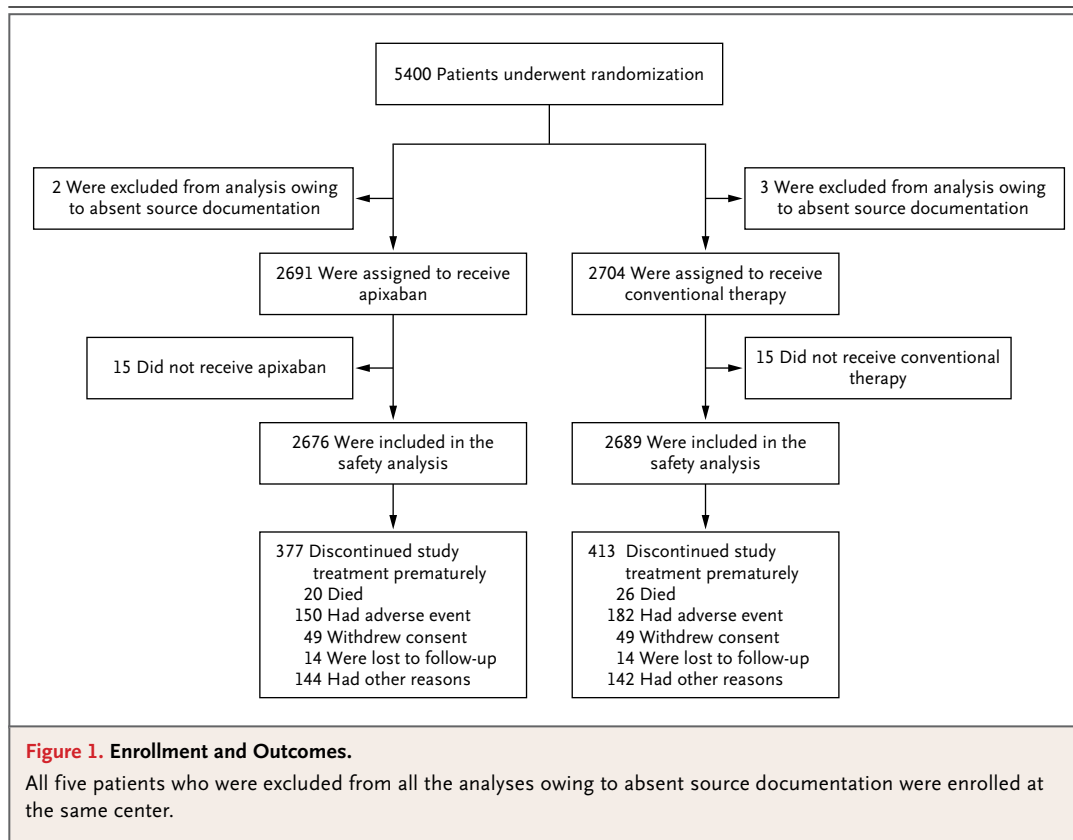ll access to the data through the sponsors. An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying diagnosis, the anatomical extent of the initial deep-vein thrombosis or pulmonary embolism, and all suspected outcomes. An independent data and safety monitoring committee periodically reviewed the study outcomes. All the members of the steering committee contributed to the interpretation of the results, wrote the first version of the manuscript and approved all versions, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data reported and the fidelity of this article to the study protocol. The protocol, with accompanying documents, is available with the full text of this article at NEJM.org.

PATIENTS

Patients were eligible for inclusion in the study if they were 18 years of age or older and had objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism (with or without deep-vein thrombosis). Proximal deep-vein thrombosis was defined as thrombosis involving at least the popliteal vein or a more proximal vein. The full list of inclusion criteria and the criteria for pulmonary embolism are provided in the Supplementary Appendix, available at NEJM.org.

Patients were excluded if they had active bleeding, a high risk of bleeding, or other contraindications to treatment with enoxaparin and warfarin; if they had cancer and long-term treatment with low-molecular-weight heparin was planned; if their deep-vein thrombosis or pulmonary embolism was provoked in the absence of a persistent risk factor for recurrence; if less than 6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin at a dose of more than 165 mg daily, or treatment with potent inhibitors of cytochrome P-450 3A4.

Patients were also excluded if they had received more than two doses of a once-daily low-molecular-weight heparin regimen, fondaparinux, or a vitamin K antagonist; more than three doses of a twice-daily low-molecular-weight heparin regimen; or more than 36 hours of continuous intravenous heparin. Additional exclusion criteria were a hemoglobin level of less than 9 mg per deciliter, a platelet count of less than 100,000 per cubic millimeter, a serum creatinine level of more than

Figure 1. Enrollment and Outcomes.

All five patients who were excluded from all the analyses owing to absent source documentation were enrolled at the same center.

2.5 mg per deciliter (220 μmol per liter), or a calculated creatinine clearance of less than 25 ml per minute. The full list of exclusion criteria is provided in the protocol.

RANDOMIZATION AND STUDY TREATMENT

Randomization was performed with the use of an interactive voice-response system and was stratified according to the qualifying diagnosis of either symptomatic proximal deep-vein thrombosis or symptomatic pulmonary embolism (with or without deep-vein thrombosis). Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets. The study regimens were to be initiated within 24 hours after randomization.

Patients assigned to the apixaban group received 10 mg of apixaban twice daily for the first 7 days, followed by 5 mg twice daily for 6 months. Patients assigned to the conventional-therapy group received enoxaparin at a dose of 1 mg per kilogram of body weight every 12 hours for at

least 5 days and warfarin begun concomitantly and continued for 6 months. The warfarin dose was adjusted to maintain the international normalized ratio (INR) between 2.0 and 3.0. Enoxaparin or placebo was discontinued when a blinded INR of 2.0 or more was achieved.

The study used blinded INR monitoring with a point-of-care device that generated an encrypted code for INR results. Investigators reported the code to the interactive voice-response system and received either an actual INR value (for patients assigned to warfarin) or a sham INR value (for patients receiving apixaban). Evaluation of the INR was required at least monthly, or more frequently if clinically indicated.

OUTCOME MEASURES

The primary efficacy outcome was the incidence of the adjudicated composite of recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. Recurrent venous thromboembolism included fatal or nonfatal pulmonary embolism and deep-vein thrombosis. Death was adjudicated as related to venous

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Apixaban (N=2691)	Conventional Therapy (N=2704)
Age — yr	57.2±16.0	56.7±16.0
Male sex — no. (%)	1569 (58.3)	1598 (59.1)
Weight		
Mean — kg	84.6±19.8	84.6±19.8
Distribution — no. (%)		
≤60 kg	231 (8.6)	245 (9.1)
>60 to <100 kg	1932 (71.8)	1936 (71.6)
≥100 kg	522 (19.4)	518 (19.2)
Data missing	6 (0.2)	5 (0.2)
Creatinine clearance — no. (%)		
≤30 ml/min	14 (0.5)	15 (0.6)
>30 to ≤50 ml/min	161 (6.0)	148 (5.5)
>50 to ≤80 ml/min	549 (20.4)	544 (20.1)
>80 ml/min	1721 (64.0)	1757 (65.0)
Data missing	246 (9.1)	240 (8.9)
Qualifying diagnosis — no. (%)		
Deep-vein thrombosis	1749 (65.0)	1783 (65.9)
Pulmonary embolism	678 (25.2)	681 (25.2)
Pulmonary embolism with deep-vein thrombosis	252 (9.4)	225 (8.3)
Could not be evaluated	12 (0.4)	15 (0.6)
Diagnostic method — no./total no. (%)†		
Deep-vein thrombosis		
Compression ultrasonography	1731/1749 (99.0)	1771/1783 (99.3)
Ascending contrast venography	20/1749 (1.1)	11/1783 (0.6)
Computed tomography	2/1749 (0.1)	1/1783 (<0.1)
Pulmonary embolism		
Spiral computed tomography	810/930 (87.1)	804/906 (88.7)
Ventilation–perfusion lung scanning	109/930 (11.7)	92/906 (10.2)
Pulmonary angiography	21/930 (2.3)	16/906 (1.8)
Most proximal location of qualifying deep-vein thrombosis — no./total no. (%)		
Popliteal vein	426/1749 (24.4)	441/1783 (24.7)
Femoral vein	570/1749 (32.6)	585/1783 (32.8)
Common femoral or iliac vein	753/1749 (43.1)	754/1783 (42.3)
Distal vein	0/1749	3/1783 (0.2)
Anatomical extent of qualifying pulmonary embolism — no./total no. (%)‡		
Limited	79/930 (8.5)	89/906 (9.8)
Intermediate	392/930 (42.2)	395/906 (43.6)
Extensive	357/930 (38.4)	326/906 (36.0)
Could not be assessed	102/930 (11.0)	96/906 (10.6)
Time from onset of symptoms to randomization — days		
Median	5.0	5.0
Interquartile range	3.0–9.0	3.0–9.0

Table 1. (Continued.)		
Characteristic	Apixaban (N = 2691)	Conventional Therapy (N = 2704)
Clinical presentation of VTE — no. (%)		
Unprovoked	2416 (89.8)	2429 (89.8)
Provoked	272 (10.1)	272 (10.1)
Not reported	3 (0.1)	3 (0.1)
Risk factors for recurrent VTE — no. (%)§		
Previous VTE	463 (17.2)	409 (15.1)
Known thrombophilia	74 (2.8)	59 (2.2)
Active cancer	66 (2.5)	77 (2.8)
Treatment with low-molecular-weight heparin, heparin, or fondaparinux before randomization — no. (%)		
None	358 (13.3)	381 (14.1)
≤12 hr	371 (13.8)	341 (12.6)
>12 to 24 hr	1116 (41.5)	1126 (41.6)
>24 to 36 hr	587 (21.8)	613 (22.7)
>36 to 48 hr	231 (8.6)	211 (7.8)
>48 hr	22 (0.8)	26 (1.0)
Data missing	6 (0.2)	6 (0.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. VTE denotes venous thromboembolism. There were no significant differences between the study groups in the baseline characteristics listed here.
† Patients may have undergone more than one imaging test.
‡ The anatomical extent of qualifying pulmonary embolism was defined as limited if it involved 25% or less of the vasculature of a single lobe, extensive if there were two or more lobes involving 50% or more of the vasculature for each lobe, and intermediate if neither of these definitions was met.
§ Patients could have had multiple risk factors or no additional risk factors.

thromboembolism, related to cardiovascular disease, caused by bleeding, or due to other causes. Pulmonary embolism was considered the cause of death if there was objective documentation or if death could not be attributed to another documented cause and pulmonary embolism could not be ruled out.

The predefined secondary efficacy outcomes included each component of the primary efficacy outcome, as well as death from cardiovascular causes and death from any cause. An additional predefined secondary outcome was the composite of symptomatic recurrent venous thromboembolism with death from cardiovascular causes, with death from any cause, or with death related to venous thromboembolism plus major bleeding.

The primary safety outcome was adjudicated major bleeding. The secondary safety outcome was the composite of major bleeding and clinically relevant nonmajor bleeding. Bleeding was defined as major if it was overt and associated with a decrease in the hemoglobin level of 2 g per deciliter or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death.[6] Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life.[7] The criteria for the diagnosis and adjudication of all outcomes are provided in the Supplementary Appendix.

SURVEILLANCE AND FOLLOW-UP

Patients underwent assessment, either in the clinic or by telephone, at weeks 2, 4, 8, 12, 16, 20, and 24 (6 months) after randomization and 30 days after the end of the intended treatment period. Patients were instructed to report to the study center if they had symptoms suggestive of recurrent venous thromboembolism or bleeding. Prespecified objective testing was required for patients in whom an outcome event was suspected.

STATISTICAL ANALYSIS

The study was designed to test the hypothesis that apixaban would be noninferior to conventional therapy with respect to the primary efficacy outcome. The criteria for noninferiority required that the upper limits of the 95% confidence intervals were below prespecified margins for both the relative risk (<1.80) and the risk difference (<3.5 percentage points).

The noninferiority margin for a relative risk of 1.8 required that apixaban preserve at least 70% of the relative reduction in the risk of recurrent venous thromboembolism associated with conventional therapy. If noninferiority was shown, testing for superiority was to be performed according to a prespecified hierarchy of outcomes: major bleeding (primary safety outcome), followed by recurrent venous thromboembolism or death related to venous thromboembolism (primary efficacy outcome), and finally, the compos-

ite of major bleeding and clinically relevant nonmajor bleeding (secondary safety outcome).

With the use of an estimated incidence of the primary efficacy outcome of 3% at 6 months with conventional therapy and a noninferiority margin of 1.80 for the relative risk, we calculated that we would need to enroll 4094 patients for the study to have 90% power to show the noninferiority of apixaban, at a one-sided alpha level of 0.025. This sample was increased to 4816 patients to account for up to 15% of patients discontinuing treatment early. The sample was increased to 5400 patients by the steering committee after a protocol-defined blinded review of the overall incidence of the primary efficacy outcome performed after 80% of patients had been enrolled.

All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented. The effect of missing outcome data was evaluated with

Table 2. Clinical Outcomes during the Intended Treatment Period.*

Outcome	Apixaban (N=2691)	Conventional Therapy (N=2704)	Relative Risk (95% CI)	P Value
Efficacy				
No. of patients	2609	2635		
First recurrent VTE or VTE-related death — no. (%)	59 (2.3)	71 (2.7)	0.84 (0.60–1.18)	<0.001†
Type of first recurrent VTE — no. (%)				
Fatal PE	1 (<0.1)	2 (0.1)		
Death for which PE could not be ruled out	11 (0.4)	13 (0.5)		
Nonfatal PE with or without DVT	27 (1.0)	23 (0.9)		
DVT only	20 (0.8)	33 (1.3)		
Safety				
No. of patients	2676	2689		
Major bleeding — no. (%)‡	15 (0.6)	49 (1.8)	0.31 (0.17–0.55)	<0.001§
Fatal bleeding¶	1 (<0.1)	2 (0.1)		
Nonfatal major bleeding at a critical site	4 (0.1)	14 (0.5)		
Intracranial	3 (0.1)	6 (0.2)		
Retroperitoneal	1 (<0.1)	3 (0.1)		
Intrathoracic	0	1 (<0.1)		
Intraocular	0	2 (0.1)		
Intraarticular	0	2 (0.1)		
Other nonfatal major bleeding	10 (0.4)	33 (1.2)		
Gastrointestinal bleeding	7 (0.3)	18 (0.7)		
Intramuscular bleeding	0	5 (0.2)		
Epistaxis	1 (<0.1)	1 (<0.1)		
Urogenital bleeding	1 (<0.1)	3 (0.1)		
Subcutaneous hematoma	1 (<0.1)	6 (0.2)		

Table 2. (Continued.)

Outcome	Apixaban (N = 2691)	Conventional Therapy (N = 2704)	Relative Risk (95% CI)	P Value
Clinically relevant nonmajor bleeding — no. (%)	103 (3.8)	215 (8.0)	0.48 (0.38–0.60)	
Major bleeding or clinically relevant nonmajor bleeding — no. (%)‡	115 (4.3)	261 (9.7)	0.44 (0.36–0.55)	<0.001
Death during intended treatment period				
No. of patients/total no. (%)	41/2676 (1.5)	52/2689 (1.9)	0.79 (0.53–1.19)	
Cause of death — no./total no. (%)				
PE or PE not ruled out	12/2676 (0.4)	16/2689 (0.6)		
Cardiovascular cause	3/2676 (0.1)	7/2689 (0.3)		
Bleeding	2/2676 (0.1)	3/2689 (0.1)		
Cancer	14/2676 (0.5)	14/2689 (0.5)		
Infectious disease	9/2676 (0.3)	7/2689 (0.3)		
Other	1/2676 (<0.1)	5/2689 (0.2)		
Secondary composite outcomes				
VTE or death from cardiovascular cause — no./total no. (%)	61/2609 (2.3)	77/2635 (2.9)	0.80 (0.57–1.11)	0.18
VTE or death from any cause — no./total no. (%)	84/2609 (3.2)	104/2635 (3.9)	0.82 (0.61–1.08)	0.16
VTE, VTE-related death, or major bleeding — no./total no. (%)	73/2609 (2.8)	118/2635 (4.5)	0.62 (0.47–0.83)	0.001
Adverse events				
Any event during treatment — no./total no. (%)	1795/2676 (67.1)	1923/2689 (71.5)		
Any serious event during treatment — no./total no. (%)	417/2676 (15.6)	410/2689 (15.2)		
Any bleeding event — no./total no. (%)	415/2676 (15.5)	695/2689 (25.8)		
Any event resulting in permanent discontinuation of study drug — no./total no. (%)	162/2676 (6.1)	199/2689 (7.4)		

* DVT denotes deep-vein thrombosis, and PE pulmonary embolism.
† The P value is for noninferiority.
‡ For patients who had more than one event, only the first event was counted.
§ The P value is for superiority.
¶ Death from gastrointestinal bleeding occurred in one patient in each group, and death from intramuscular bleeding in one patient in the conventional-therapy group.

the use of a sensitivity analysis (see the Supplementary Appendix). All safety analyses included data obtained from patients during study treatment, defined as the time from the administration of the first dose until 48 hours after the last dose was administered. Prespecified subgroup analyses were performed for subgroups defined by the qualifying diagnosis at study entry (deep-vein thrombosis or pulmonary embolism), and the quartile of the mean time in the therapeutic range for the INR, as determined at each study center. The time in the therapeutic range was calculated with the use of standard methods[8] beginning on day 15 of therapy and was corrected for planned interruptions of therapy.
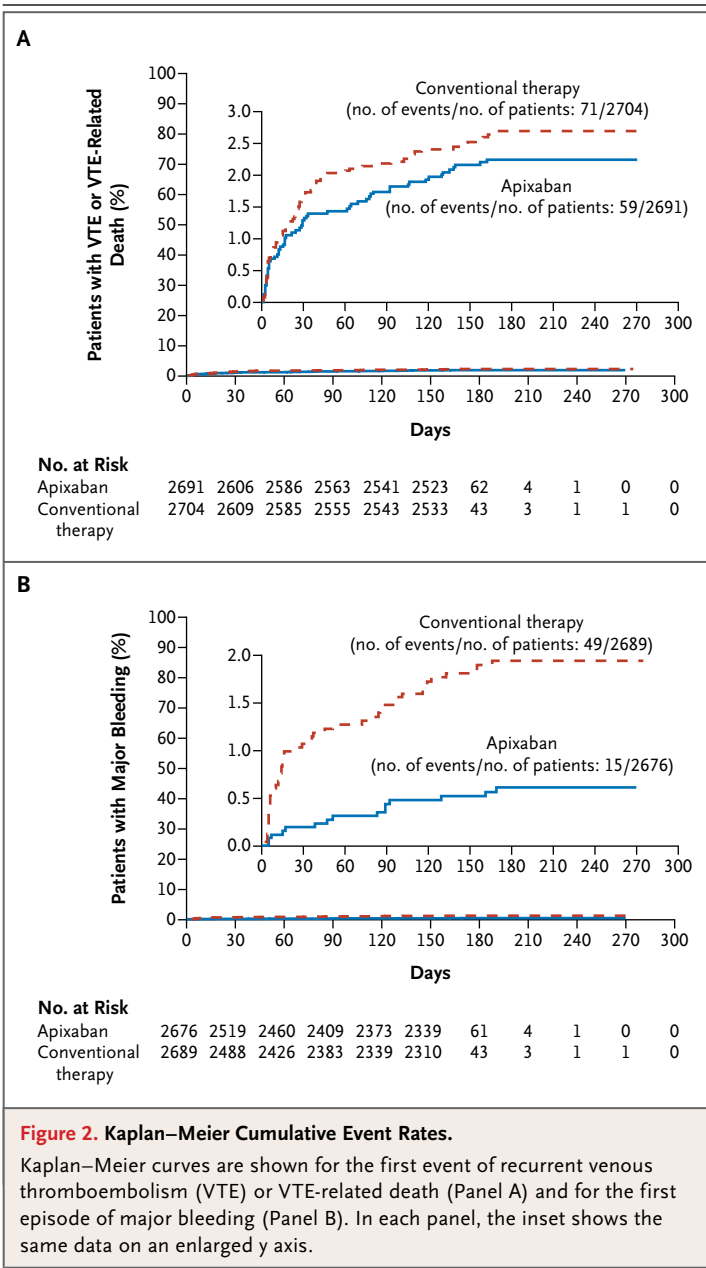
The 95% confidence interval for the relative risk was calculated with the use of the Mantel–Haenszel method, stratified according to the qualifying diagnosis (deep-vein thrombosis or pulmonary embolism). The 95% confidence interval for the difference in risk was calculated for the primary outcome with the use of the inverse-variance method.[9] Statistical testing for noninferiority was performed with the method of Farrington and Manning.[10] Time-to-event curves were calculated with the Kaplan–Meier method.

RESULTS

PATIENTS

From August 2008 through August 2012, a total of 5400 patients were enrolled at 358 centers in

Figure 2. Kaplan–Meier Cumulative Event Rates.

Kaplan–Meier curves are shown for the first event of recurrent venous thromboembolism (VTE) or VTE-related death (Panel A) and for the first episode of major bleeding (Panel B). In each panel, the inset shows the same data on an enlarged y axis.

28 countries (Fig. 1). The baseline characteristics of the patients in the two study groups were similar (Table 1).

TREATMENT

In the conventional-therapy group, the median duration of enoxaparin treatment was 6.5 days (interquartile range, 5.0 to 8.0). The INR was in the therapeutic range (2.0 to 3.0) 61% of the time, was above 3.0 for 16% of the time, and was below 2.0 for 23% of the time. In the apixaban group,

adherence to therapy was 80% or more in 96% of the patients.

CLINICAL OUTCOMES

The primary efficacy outcome of recurrent venous thromboembolism occurred in 59 of 2609 patients (2.3%) in the apixaban group and in 71 of 2635 (2.7%) in the conventional-therapy group, for a relative risk with apixaban of 0.84 (95% confidence interval [CI], 0.60 to 1.18; P<0.001 for noninferiority). The difference in risk (apixaban minus conventional therapy) was −0.4 percentage points (95% CI, −1.3 to 0.4; P<0.001 for noninferiority). A sensitivity analysis in which all patients with missing outcome data were assumed to have had an event did not alter the results for noninferiority. The types of recurrent thromboembolic events are shown in Table 2.

Among patients who had deep-vein thrombosis at enrollment, the primary efficacy outcome occurred in 38 of 1698 patients (2.2%) in the apixaban group and in 47 of 1736 (2.7%) in the conventional-therapy group (relative risk, 0.83; 95% CI, 0.54 to 1.26; difference in risk [apixaban minus conventional therapy], −0.5 percentage points; 95% CI, −1.5 to 0.6). Among patients who had pulmonary embolism at enrollment, the primary efficacy outcome occurred in 21 of 900 patients (2.3%) in the apixaban group and in 23 of 886 (2.6%) in the conventional-therapy group (relative risk, 0.90; 95% CI, 0.50 to 1.61; difference in risk, −0.3 percentage points; 95% CI, −1.7 to 1.2).

Major bleeding occurred in 15 of 2676 patients (0.6%) in the apixaban group and in 49 of 2689 (1.8%) in the conventional-therapy group, for a relative risk of 0.31 (95% CI, 0.17 to 0.55; P<0.001 for superiority). The difference in risk was −1.1 percentage points (95% CI, −1.7 to −0.6). The results for the composite of major bleeding and clinically relevant nonmajor bleeding and for the other secondary outcomes are provided in Table 2.

The Kaplan–Meier curves for the first event of recurrent venous thromboembolism and the first major bleeding episode are shown in Figure 2A and 2B, respectively. The results of the subgroup analyses for the primary efficacy and safety outcomes are provided in Figure S1A and S1B, respectively, in the Supplementary Appendix. The efficacy and safety results according to the quartile of the mean time in the therapeutic range for the INR are shown in Figure S2 in the Supplementary Appendix.

During the 30-day follow-up after the intended treatment period, recurrent venous thromboembolism occurred in six patients (0.2%) who had received apixaban and in nine (0.3%) who had received conventional therapy. The rates of adverse events, including elevations in liver-function tests, were similar in the two treatment groups (Table 2, and Table S2 in the Supplementary Appendix).

DISCUSSION

For the treatment of acute venous thromboembolism, the AMPLIFY study showed that a fixed-dose regimen of oral apixaban alone was as effective as conventional treatment consisting of enoxaparin followed by warfarin and was associated with a clinically relevant reduction of 69% in major bleeding.

These findings add to the evidence that the new oral anticoagulants are simple alternatives to conventional therapy for patients with acute venous thromboembolism[3,4,11] and address some lingering clinical questions. One question concerns the efficacy of these agents in patients with pulmonary embolism or with extensive venous thromboembolism. The efficacy of apixaban in the patients with pulmonary embolism was similar to that in the patients with deep-vein thrombosis, and the relative effect was maintained in the approximately 40% of patients who presented with extensive disease. A second question concerns the efficacy and safety of the new agents relative to well-controlled warfarin therapy.[12] Even for study centers where the mean time in the therapeutic range with warfarin exceeded 68%, the efficacy and the reduction in major bleeding with apixaban were consistent with the overall findings.

Several aspects of the study reinforce the validity of our findings. The efficacy and safety of apixaban were consistent across a broad range of subgroups, including those based on clinically important features such as an age of more than 75 years, a body weight of more than 100 kg, use of parenteral anticoagulant treatment before randomization, and the duration of such treatment. The reduction in major bleeding was paralleled by a decrease in clinically relevant nonmajor bleeding, which provides further evidence for the safety of this apixaban regimen.

Methodologic strengths of the study include the minimization of bias with the double-blind design, identical follow-up of all patients, and central adjudication of all outcome events. Study execution was rigorous, with minimal loss to follow-up, few patients withdrawing consent, good adherence to study medication, and well-managed warfarin therapy.

The results of this trial are likely to be generalizable. We recruited a wide spectrum of patients, most of whom had unprovoked venous thromboembolism, and the rates of major bleeding and clinically relevant nonmajor bleeding with warfarin were similar to those reported in other studies.[3,4,11] However, additional information is needed about the efficacy and safety of apixaban in patients with cancer, low body weight, or a creatinine clearance of less than 50 ml per minute.

On the basis of the results of this study, together with those of the Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism trial,[5] apixaban provided a simple, effective, and safe regimen for the initial and long-term treatment of venous thromboembolism.

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