

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 21, 2013

VOL. 368 NO. 8

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

ABSTRACT

BACKGROUND

Apixaban, an oral factor Xa inhibitor that can be administered in a simple, fixed-dose regimen, may be an option for the extended treatment of venous thromboembolism.

METHODS

In this randomized, double-blind study, we compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy. The study drugs were administered for 12 months.

RESULTS

A total of 2486 patients underwent randomization, of whom 2482 were included in the intention-to-treat analyses. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 73 of the 829 patients (8.8%) who were receiving placebo, as compared with 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% confidence interval [CI], 5.0 to 9.3) and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1) ($P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.

CONCLUSIONS

Extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding. (Funded by Bristol-Myers Squibb and Pfizer; AMPLIFY-EXT ClinicalTrials.gov number, NCT00633893.)

From the Department of Internal and Cardiovascular Medicine–Stroke Unit, University of Perugia, Perugia, Italy (G.A.); the Academic Medical Center, Department of Vascular Medicine, Amsterdam (H.R.B.); King's College Hospital, London (A.C.); Pfizer, Groton, CT (M.C., M.J., A.P.); Flinders Medical Centre and Flinders University, Department of Haematology, Adelaide, SA, Australia (A.S.G.); the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); and the Departments of Medicine and Biochemistry and Biomedical Sciences, McMaster University, and the Thrombosis and Atherosclerosis Research Institute — both in Hamilton, ON, Canada (J.I.W.). Address reprint requests to Dr. Agnelli at the University of Perugia, Piazzale Menghini 1, 06100 Perugia, Italy, or at agnelli@unipg.it.

*Additional investigators and committees for the Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment (AMPLIFY-EXT) study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on December 8, 2012, at NEJM.org.

N Engl J Med 2013;368:699–708.

DOI: 10.1056/NEJMoa1207541

Copyright © 2012 Massachusetts Medical Society.

VENOUS THROMBOEMBOLISM, WHICH INCLUDES deep-vein thrombosis and pulmonary embolism, is the third most common cause of vascular disease–related deaths.¹ The mainstay of treatment is anticoagulation, and guidelines recommend therapy for 3 months or longer.^{2,3} Decisions about extending treatment are challenging. Although warfarin is effective for the prevention of recurrent venous thromboembolism, the inconvenience of laboratory monitoring and the dietary restrictions, coupled with concerns about bleeding, often lead to a reluctance to continue warfarin therapy beyond 6 to 12 months. Attempts to reduce the risk of bleeding by lowering the intensity of warfarin therapy have resulted in decreased efficacy without less bleeding.^{4,5}

If warfarin is discontinued, the risk of recurrent venous thromboembolism is 6 to 10% per year in patients without reversible risk factors.^{6–9} In addition, such patients are at increased risk for arterial thrombotic events, such as myocardial infarction, stroke, and vascular death,^{1,10,11} and the rate of these events may also be reduced with anticoagulation therapy.¹²

Apixaban is an oral factor Xa inhibitor that is administered in fixed doses without the need for laboratory monitoring. At a dose of 5 mg twice daily, apixaban has been shown to be effective for the prevention of stroke in patients with atrial fibrillation, and at a dose of 2.5 mg twice daily, the lowest dose evaluated in phase 2 studies, it has been shown to be effective for thromboprophylaxis after major orthopedic surgery.^{13–15} In the Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment (AMPLIFY-EXT) study, we compared the efficacy and safety of these two doses of apixaban with those of placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom treating physicians were uncertain about continuing therapy. Additional aims of the study were to determine whether the lower dose of apixaban was effective and whether it was associated with less bleeding than the higher dose and to examine the effect of treatment on arterial thrombotic outcomes.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted a randomized, double-blind study comparing the efficacy and safety of two doses of apixaban with those of placebo for the extended treatment of venous thromboembolism. The trial was sponsored by Bristol-Myers Squibb and Pfizer. The steering committee, comprising both academic and sponsor authors, had final responsibility for the design of the study, the development of the protocol, the oversight of the study, the verification of the data, and the analyses. The protocol was approved by the institutional review board at each participating center and is available with the full text of this article at NEJM.org. Written informed consent was obtained from all the patients. The sponsors collected and maintained the data; the academic authors had access to the data at all times, through the sponsors. An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying initial diagnosis (deep-vein thrombosis or pulmonary embolism) and all suspected outcomes. An independent data monitoring committee periodically reviewed the study outcomes. All members of the steering committee contributed to the interpretation of the results, wrote and approved all versions of the manuscript and made the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of this article to the study protocol.

PATIENTS

Patients were eligible for inclusion in the study if they were 18 years of age or older; if they had objectively confirmed, symptomatic deep-vein thrombosis or pulmonary embolism (with or without deep-vein thrombosis); if they had been treated for 6 to 12 months with standard anticoagulant therapy or had completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial (ClinicalTrials.gov number, NCT00643201); if they had not had a symptomatic recurrence during prior anticoagulant therapy; and if there was clinical equipoise about the continuation or cessation of anticoagulant therapy.

Patients were ineligible if they had a contraindication to continued anticoagulant therapy or if they required ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose higher than 165 mg daily. Additional ineligibility criteria included 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 2.5 mg per deciliter (221 μ mol per liter) or a calculated creatinine clearance of less than 25 ml per minute, an alanine aminotransferase or aspartate aminotransferase level that was more than 2 times the upper limit of the normal range, or a total bilirubin level that was more than 1.5 times the upper limit of the normal range. The full list of exclusion criteria is provided in the protocol.

RANDOMIZATION

Randomization was performed with the use of an interactive voice-response system and was stratified according to the initial diagnosis (deep-vein thrombosis or pulmonary embolism) and participation or no participation in the AMPLIFY trial. Patients were enrolled within approximately 7 days after they received the last dose of prior anticoagulant therapy and, if they were receiving a vitamin K antagonist, when the international normalized ratio was 2.0 or lower.

Patients were assigned, in a 1:1:1 ratio, to receive 2.5 mg of apixaban, 5 mg of apixaban, or placebo, all given twice daily. The intended duration of administration of the study drug was 12 months. During the course of the trial, dual antiplatelet therapy, aspirin at a dose higher than 165 mg daily, and potent inhibitors of cytochrome P-450 3A4 and P-glycoprotein were prohibited.

OUTCOME MEASURES

The primary efficacy outcome was the composite of symptomatic recurrent venous thromboembolism or death from any cause — an outcome consistent with that recommended in regulatory guidelines for trials of extended treatment for venous thromboembolic diseases.¹⁶ Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Death was classified as related to venous thromboembolism, related to cardiovas-

cular disease, due to bleeding, or due to other causes.

Symptomatic recurrent venous thromboembolism or death related to venous thromboembolism was a prespecified secondary efficacy outcome. A report¹¹ published after the trial began prompted the addition of another secondary outcome before the database was locked and the data were unblinded — the composite of symptomatic recurrent venous thromboembolism, death related to venous thromboembolism, myocardial infarction, stroke, or death related to cardiovascular disease. The criteria for the diagnosis and adjudication of efficacy outcomes and their components are described in the protocol and in the Supplementary Appendix, available at NEJM.org.

The primary safety outcome was major bleeding. The secondary safety outcome was the composite of major or clinically relevant nonmajor bleeding. Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death.^{6,7} Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but that was associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living¹⁷ (further details are provided in the Supplementary Appendix). Net clinical benefit was defined as a reduction in the composite of symptomatic recurrent venous thromboembolism, death related to venous thromboembolism, myocardial infarction, stroke, death related to cardiovascular disease, or major bleeding.

SURVEILLANCE AND FOLLOW-UP

Patients underwent assessment, either in the clinic or by telephone, monthly during the intended treatment period and 30 days after the end of the 1-year intended study 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.

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

Characteristic	Apixaban, 2.5 mg (N = 840)	Apixaban, 5 mg (N = 813)	Placebo (N = 829)
Age — yr	56.6±15.3	56.4±15.6	57.1±15.2
Male sex — no. (%)	487 (58.0)	469 (57.7)	468 (56.5)
Weight			
Mean — kg	85.7±19.8	85.7±19.1	84.7±18.6
Distribution — no. (%)			
≤60 kg	58 (6.9)	59 (7.3)	48 (5.8)
>60 kg	780 (92.9)	751 (92.4)	778 (93.8)
Data missing	2 (0.2)	3 (0.4)	3 (0.4)
Creatinine clearance — no. (%)			
≤30 ml/min	1 (0.1)	3 (0.4)	2 (0.2)
>30 to ≤50 ml/min	47 (5.6)	41 (5.0)	44 (5.3)
>50 to ≤80 ml/min	174 (20.7)	168 (20.7)	194 (23.4)
>80 ml/min	595 (70.8)	580 (71.3)	564 (68.0)
Data missing	23 (2.7)	21 (2.6)	25 (3.0)
Initial diagnosis — no. (%)			
Deep-vein thrombosis	544 (64.8)	527 (64.8)	551 (66.5)
Pulmonary embolism	296 (35.2)	286 (35.2)	278 (33.5)
Clinical presentation of VTE at initial diagnosis — no. (%)			
Unprovoked	783 (93.2)	737 (90.7)	755 (91.1)
Associated with transient or reversible risk factor	56 (6.7)	76 (9.3)	72 (8.7)
Risk factors for recurrent VTE — no. (%)†			
Active cancer	15 (1.8)	9 (1.1)	18 (2.2)
Persistent or permanent immobilization	19 (2.3)	29 (3.6)	22 (2.7)
Previous deep-vein thrombosis or pulmonary embolism	99 (11.8)	118 (14.5)	99 (11.9)
Known prothrombotic genotype	32 (3.8)	26 (3.2)	36 (4.3)
Use of antiplatelet agents‡	120 (14.3)	96 (11.8)	107 (13.0)

* Plus-minus values are means ±SD. There were no significant differences among the study groups in the baseline characteristics listed here. VTE denotes venous thromboembolism.

† Patients could have multiple risk factors.

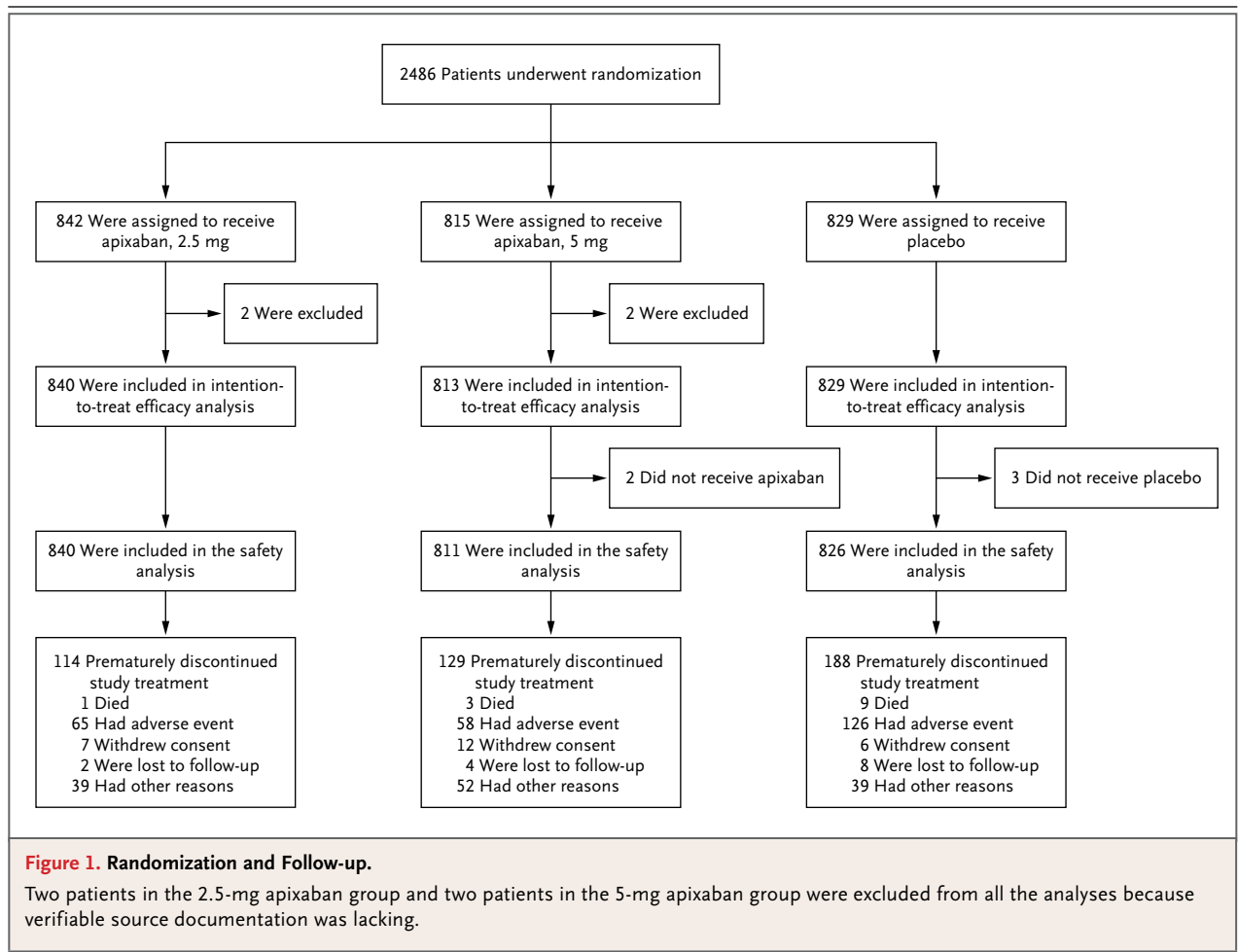
‡ Data on the use of antiplatelet agents were calculated in the safety population (840 patients in the 2.5-mg apixaban group, 811 in the 5-mg apixaban group, and 826 in the placebo group), rather than the intention-to-treat population.

STATISTICAL ANALYSIS

The study was designed to test the hypothesis that each dose of apixaban would be superior to placebo with respect to the primary efficacy outcome. Assuming an estimated incidence in the placebo group of 6.8% at 12 months and a decrease in the primary outcome of 41% with active treatment as compared with placebo,^{18,19} we calculated that we would need to enroll 810 patients in each group for the study to have 90% power to show the superiority of apixaban over placebo, at a two-sided alpha level of 0.05, with the use of the Hochberg multiple-testing method.²⁰

All efficacy analyses included data from the intention-to-treat population during the 12-month active study period. All safety analyses included data from patients during the time they were receiving treatment, which was defined as the time between administration of the first dose of a study drug and 48 hours after administration of the last dose.

For the primary efficacy analysis, in accordance with agreements with regulatory authorities, patients who were lost to follow-up were classified as having had a primary outcome event. For the analyses of the secondary outcomes and



for the safety analyses, patients who were lost to follow-up were classified as not having had an outcome event.

In the analyses of efficacy and safety, the proportions of outcome events in the two groups were compared with the use of the Cochran–Mantel–Haenszel test, stratified according to the initial diagnosis (deep-vein thrombosis or pulmonary embolism). The time-to-event curves were calculated with the use of the Kaplan–Meier method.

RESULTS

PATIENTS

From May 2008 through July 2011, a total of 2486 patients were enrolled at 328 sites in 28 countries. Two patients in the 2.5-mg apixaban group and 2 patients in the 5-mg apixaban group were

excluded from all the analyses because verifiable source documentation was lacking for them. The characteristics of patients in the three study groups were similar at baseline (Table 1). Figure 1 shows the random assignment and follow-up of the patients.

EFFICACY

During the 1-year active study period, a primary efficacy outcome event occurred in 96 of the 829 patients who were receiving placebo (11.6%), 32 of the 840 patients who were receiving 2.5 mg of apixaban (3.8%), and 34 of the 813 patients who were receiving 5 mg of apixaban (4.2%) (Table 2). A total of 19 patients in the placebo group (2.3%), 13 patients in the 2.5-mg apixaban group (1.5%), and 20 patients in the 5-mg apixaban group (2.5%) were lost to follow-up and were counted as having had a primary outcome event. Both

Table 2. Clinical Outcomes in the Intention-to-Treat Population during the Intended Active Study Period.*

Outcome	Apixaban, 2.5 mg (N=840)	Apixaban, 5 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI)		
				Apixaban, 2.5 mg, vs. Placebo	Apixaban, 5 mg, vs. Placebo	Apixaban, 2.5 mg vs. 5 mg
	number (percent)					
Recurrent VTE or death from any cause — primary efficacy outcome†	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22–0.48)	0.36 (0.25–0.53)	NA
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34)	0.97 (0.46–2.02)
Non–VTE-related cardiovascular death, myocardial infarction, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47(0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, myo- cardial infarction, stroke, or cardio- vascular disease–related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)
Major bleeding	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09–2.64)	0.25 (0.03–2.24)	1.93 (0.18–21.25)
Clinically relevant nonmajor bleeding	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72–2.33)	1.82 (1.05–3.18)	0.71 (0.43–1.18)
Major or clinically relevant nonmajor bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69–2.10)	1.62 (0.96–2.73)	0.74 (0.46–1.22)
VTE, VTE-related death, myocardial infar- ction, stroke, cardiovascular disease– related death, or major bleeding‡	20 (2.4)	20 (2.5)	86 (10.4)	0.23 (0.14–0.37)	0.24 (0.15–0.38)	0.97 (0.52–1.79)

* For patients who had more than one event, only the first event was considered. NA denotes not available.

† In the 2.5-mg apixaban group, 13 patients who were lost to follow-up were classified as having had a primary outcome event; in the 5-mg apixaban group, 20 patients who were lost to follow-up were classified as having had a primary outcome event; and in the placebo group, 19 patients who were lost to follow-up were classified as having had a primary outcome event.

‡ A reduction in this composite outcome was considered to represent the net clinical benefit.

apixaban doses were superior to placebo with respect to the primary outcome (difference between placebo and 2.5 mg of apixaban, 7.8 percentage points [95% confidence interval (CI), 5.5 to 10.3] and difference between placebo and 5 mg of apixaban, 7.4 percentage points [95% CI, 4.8 to 10.0]; $P < 0.001$ for both comparisons).

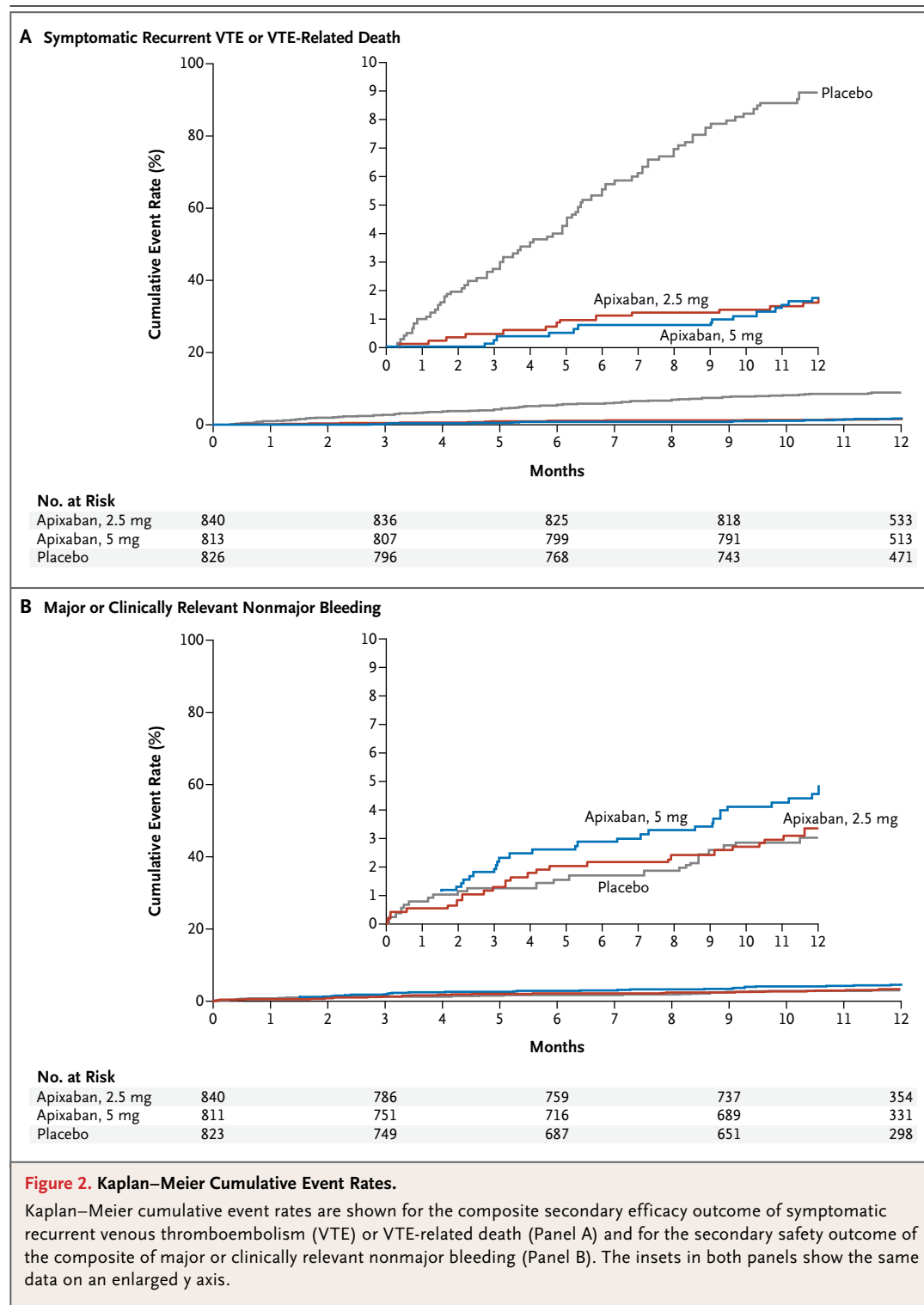
Symptomatic recurrent venous thromboembolism or death related to venous thromboembolism occurred in 73 patients (8.8%) who were receiving placebo, as compared with 14 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% CI, 5.0 to 9.3; $P < 0.001$) and 14 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1; $P < 0.001$). The difference in the rate of this outcome with the 2.5-mg dose as compared with the 5-mg dose was -0.2 percentage points (95% CI, -1.4 to 1.0). Figure 2A shows the time course of symptomatic recurrent venous thromboembolism and death related to venous thromboembolism. Results of the analysis of the combined outcome of all

thromboembolic events (symptomatic recurrent venous thromboembolism, death related to venous thromboembolism, myocardial infarction, stroke, or death related to cardiovascular disease) are shown in Table 2.

BLEEDING

Major bleeding occurred in four patients (0.5%) who were receiving placebo, as compared with two patients (0.2%) who were receiving 2.5 mg of apixaban (a difference of 0.2 percentage points; 95% CI, -0.3 to 0.8) and one patient (0.1%) who was receiving 5 mg of apixaban (a difference of 0.4 percentage points; 95% CI, -0.2 to 0.9). The difference in the rate of major bleeding with the 2.5-mg dose as compared with the 5-mg dose was 0.1 percentage points (95% CI, -0.3 to 0.5).

Clinically relevant nonmajor bleeding occurred in 19 patients (2.3%) who were receiving placebo, as compared with 25 patients (3.0%) who were receiving 2.5 mg of apixaban (a difference of -0.7 percentage points; 95% CI, -2.2 to 0.9) and 34 patients (4.2%) who were receiving 5 mg



of apixaban (a difference of -1.9 percentage points; 95% CI, -3.6 to -0.2). The difference in the rate of this outcome with the 2.5-mg dose as compared with the 5-mg dose was -1.2 percentage points (95% CI, -3.0 to 0.6). The results of the analysis of the composite

outcome of major bleeding or clinically relevant nonmajor bleeding are shown in Table 2. Figure 2B shows the time course of this composite outcome.

OTHER OUTCOMES

The composite outcome of symptomatic recurrent venous thromboembolism, death related to venous thromboembolism, myocardial infarction, stroke, death related to cardiovascular disease, or major bleeding occurred in 86 patients (10.4%) who were receiving placebo, as compared with 20 patients (2.4%) who were receiving 2.5 mg of apixaban (a difference of 8.1 percentage points; 95% CI, 5.8 to 10.4) and 20 patients (2.5%) who were receiving 5 mg of apixaban (a difference of 7.9 percentage points; 95% CI, 5.6 to 10.2). The difference in the rate of this composite outcome with the 2.5-mg dose as compared with the 5-mg dose was -0.2 percentage points (95% CI, -1.7 to 1.3). The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% and 0.5% in the 2.5-mg and 5-mg apixaban groups, respectively.

The rates of adverse events were similar in the three study groups (Table S3 in the Supplementary Appendix). Results of prespecified subgroup analyses of the efficacy outcomes (Fig. 3, and Fig. S1 in the Supplementary Appendix) and the bleeding outcomes (Fig. S2 in the Supplementary Appendix) were consistent with the observed overall treatment effects.

FOLLOW-UP AFTER THE END OF THE ACTIVE STUDY PERIOD

During the 30-day follow-up of the patients after the end of the active study period, symptomatic recurrent venous thromboembolism occurred in two patients (0.2%) who had received placebo, three patients (0.4%) who had received 2.5 mg of apixaban, and five patients (0.6%) who had received 5 mg of apixaban. The composite outcome of myocardial infarction, stroke, or death related to cardiovascular disease occurred in two patients during the follow-up period: one who had received the lower dose of apixaban and one who had received the higher dose.

DISCUSSION

This study showed that, as compared with placebo, both the 2.5-mg dose and the 5-mg dose of apixaban reduced the risk of recurrent venous

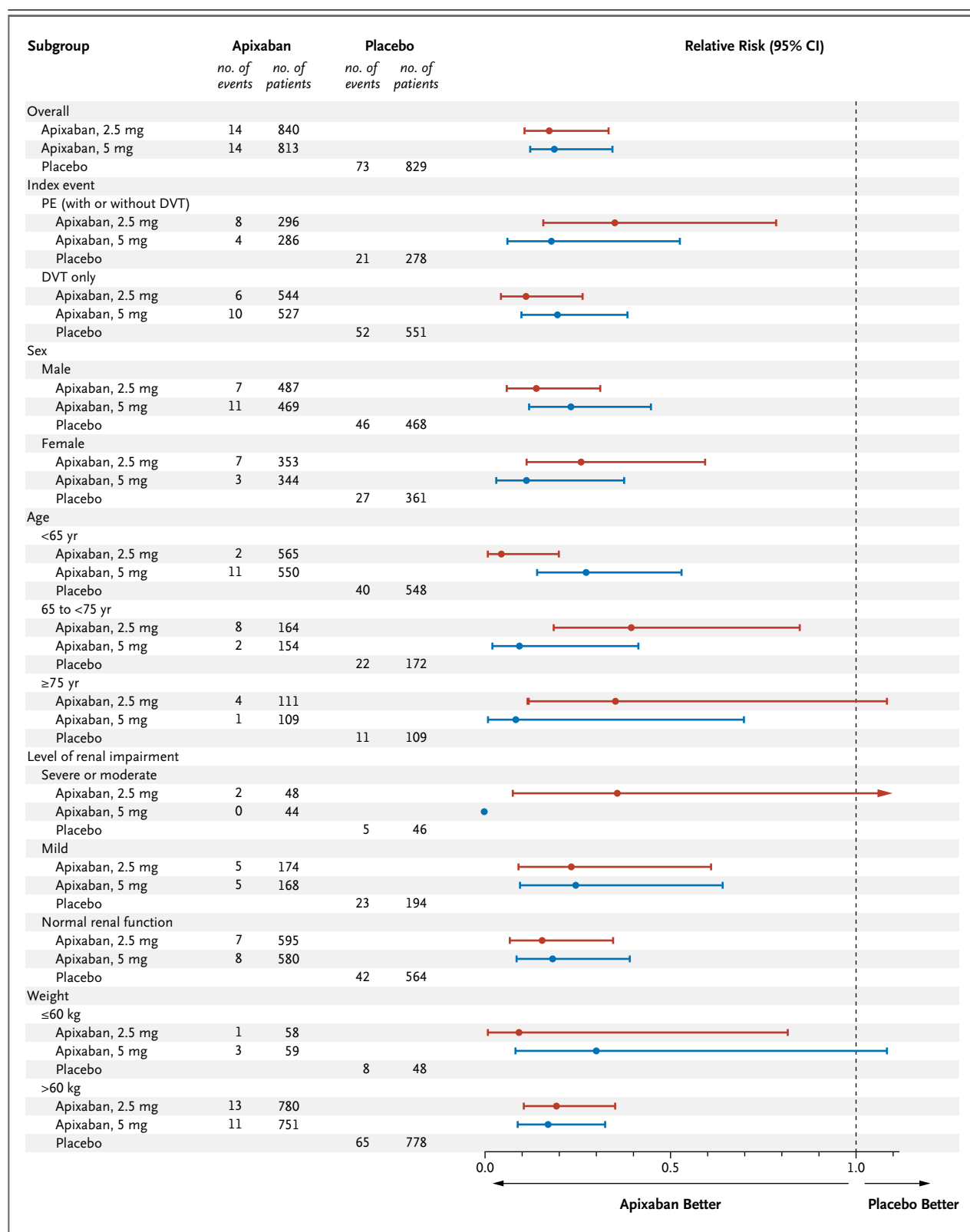
Figure 3 (facing page). Relative Risk of the Composite Secondary Efficacy Outcome of Symptomatic Recurrent Venous Thromboembolism or Death Related to Venous Thromboembolism, According to Prespecified Subgroups.

DVT denotes deep-vein thrombosis, and PE pulmonary embolism.

thromboembolism (fatal or nonfatal). These benefits were observed with rates of major bleeding that were low and similar to those in the placebo group.

The inclusion of a group that did not receive apixaban strengthens this study because it allows for an assessment of the efficacy and safety of the two doses of apixaban relative to the efficacy and safety of placebo. Although the inclusion of a placebo group could be criticized, patients who were enrolled in the trial had already received anticoagulation therapy for 6 to 12 months, and the entry criteria mandated clinical equipoise regarding the continuation or cessation of therapy. Furthermore, patients who required continued anticoagulation, such as those with atrial fibrillation or the antiphospholipid syndrome, were excluded. Given that the proportion of patients with recurrent thromboembolism (fatal or nonfatal) in the placebo group was 8.8%, it is evident that these entry criteria identified patients with an appreciable risk of recurrence.

What are the implications of these findings? For patients with venous thromboembolism for whom there is uncertainty about the benefits and risks of continued therapy, the results of this study provide a rationale for continuing anticoagulation therapy for an additional 12 months, because both the 2.5-mg twice-daily regimen of apixaban and the 5-mg twice-daily regimen were effective, safe, and simple to use. The number of patients who would need to be treated to prevent one episode of recurrent venous thromboembolism (fatal or nonfatal) during the 1-year active study period was only 14, whereas the number needed for treatment to cause one episode of major or clinically relevant nonmajor bleeding was 200. It should be noted, however, that only 15% of the patients in this study were older than 75 years of age and few had a body weight below 60 kg or moderate or severe renal impairment. Consequently, more data are needed to better determine the benefit-to-risk profile of apixaban with respect to bleeding in such patients.



Additional studies will be needed to determine the potential net benefit and risk of extending treatment beyond 18 to 24 months. The reduction in arterial thrombotic events observed with apixaban raises the possibility that such events are part of the continuing risk of thrombosis in patients with venous thromboembolism.^{10,11}

Supported by Bristol-Myers Squibb and Pfizer.

Dr. Agnelli reports receiving consulting fees from Bayer, Boehringer Ingelheim, and Daiichi Sankyo and lecture fees from Bayer Healthcare, Bristol-Myers Squibb, and Sanofi-Aventis; Dr. Buller, receiving payment for board membership and for manuscript preparation and consulting fees through his institution from Bayer and Daiichi Sankyo; Dr. Cohen, receiving payment for board membership from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, Portola, and Sanofi-Aventis and consulting fees, lecture fees, travel support, and payment

for the development of educational presentations from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Johnson & Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi-Aventis, Schering-Plough, and Takeda; Drs. Curto, Johnson, and Porcari, being employed by and having an equity interest in Pfizer; Dr. Gallus, receiving consulting fees from Bristol-Myers Squibb, Bayer, Daiichi Sankyo, Boehringer Ingelheim, and Pfizer; Dr. Raskob, receiving consulting fees, directly and through his institution, from Daiichi Sankyo, Bayer, Johnson & Johnson, Janssen, Takeda, Quintiles, and Sanofi-Aventis, receiving lecture fees, directly and through his institution, from Pfizer, Bayer, and Janssen, and receiving payment for manuscript preparation, directly and through his institution, from Bristol-Myers Squibb, Daiichi Sankyo, Sanofi-Aventis, and Bayer; and Dr. Weitz, receiving consulting fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Merck, Daiichi Sankyo, Janssen, and Pfizer. No other potential conflict of interest relevant to this article was reported.

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

REFERENCES

- Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012;379:1835-46.
- Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276-315.
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis. 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:Suppl:e419S-e494S.
- Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425-34.
- Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;349:631-9.
- Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012;366:1959-67. [Erratum, *N Engl J Med* 2012;367:1573.]
- The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-510.
- Schulman S, Baanstra D, Eriksson H, et al. Dabigatran vs. placebo for extended maintenance therapy of venous thromboembolism. *J Thromb Haemost* 2011;9:Suppl 2:22. abstract.
- Middeldorp S. Duration of anticoagulation for venous thromboembolism. *BMJ* 2011;342:d2758.
- Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalization due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet* 2007;370:1773-9.
- Becattini C, Vedovati MC, Ageno W, Dentali F, Agnelli G. Incidence of arterial cardiovascular events after venous thromboembolism: a systematic review and a meta-analysis. *J Thromb Haemost* 2010;8:891-7.
- Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol* 2003;41:Suppl S: 62S-69S.
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
- Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806-17.
- Raskob GE, Gallus AS, Pineo GF, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. *J Bone Joint Surg Br* 2012;94:257-64.
- Note for guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease. London: European Agency for the Evaluation of Medicinal Products, December 1999. (Document no. CPMP/EWP/563/98.)
- The van Gogh Investigators. Idaraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007;357:1094-104.
- Schulman S, Wähländer K, Lundström T, Clason SB, Eriksson H. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003;349:1713-21.
- The van Gogh Investigators. Extended prophylaxis of venous thromboembolism with idaraparinux. *N Engl J Med* 2007;357:1105-12.
- Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;75:800-2.

Copyright © 2012 Massachusetts Medical Society.

NEJM CLINICAL PRACTICE CENTER

Explore a new page designed specifically for practicing clinicians, the NEJM Clinical Practice Center, at www.NEJM.org/clinical-practice-center. Find practice-changing research, reviews from our Clinical Practice series, a curated collection of clinical cases, and interactive features designed to hone your diagnostic skills.