The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 30, 2017 VOL. 376 NO. 13

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

ABSTRACT

BACKGROUND

Although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

METHODS

In this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

RESULTS

A total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups.

CONCLUSIONS

Among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Weitz at the Thrombosis and Atherosclerosis Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at weitzj@taari.ca.

*A list of the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 18, 2017, at NEJM.org.

N Engl J Med 2017;376:1211-22.
DOI: 10.1056/NEJMoa1700518

Venous thromboembolism, which includes deep-vein thrombosis and pulmonary embolism, is the third most common cause of vascular death after myocardial infarction and stroke.[1-3] The mainstay of treatment is anticoagulation,[4] and in patients without active cancer, guidelines suggest the use of direct oral anticoagulant agents such as rivaroxaban over vitamin K antagonists such as warfarin.[4] Anticoagulation therapy is administered for 3 months or longer, depending on the balance between the risk of recurrent venous thromboembolism and the risk of bleeding.[4] In patients without reversible risk factors, the risk of recurrent venous thromboembolism is as much as 10% in the first year if anticoagulation therapy is stopped.[5-9] Patients in whom thrombosis was triggered by nonsurgical risk factors or who have persistent risk factors are at higher risk for recurrence than are those with postoperative thrombosis.[10] In addition, because of overlapping risk factors, patients with venous thromboembolism are at increased risk for arterial thrombotic events, including myocardial infarction, stroke, and vascular death.[11-13] Although extended anticoagulation therapy is effective for the prevention of recurrent venous thromboembolism,[5-9] concern about bleeding often leads to a reluctance to continue anticoagulant treatment beyond 6 to 12 months. Attempts to reduce the risk of bleeding when treatment is extended include the use of lower-dose anticoagulant therapy and the use of aspirin in place of an anticoagulant agent.[6,12-14]

At a dose of 20 mg once daily, rivaroxaban is effective for stroke prevention in patients with atrial fibrillation[15] and for the treatment of venous thromboembolism after an initial 21-day course of higher-dose therapy.[7,16,17] At a dose of 10 mg once daily, rivaroxaban provides effective thromboprophylaxis after elective hip or knee arthroplasty.[18-21] In the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) trial,[22] we compared the efficacy and safety of these two doses of rivaroxaban with those of aspirin in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was equipoise regarding the need for continued anticoagulation. Secondary aims of the study were to determine whether the lower dose of rivaroxaban was as effective as the higher dose and whether it was associated with less bleeding.

Methods

Study Design and Oversight

We conducted a randomized, double-blind, phase 3 study comparing the efficacy and safety of two doses of rivaroxaban with those of aspirin for the extended treatment of venous thromboembolism for up to 1 year after the initial 6 to 12 months of therapy.[22] The trial was sponsored by Bayer Pharmaceuticals. The steering committee, which included both academic authors and those employed by the sponsor, 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 sponsor collected, maintained, and analyzed the data; the academic authors had access to the data at all times through the sponsor. The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating center. Written informed consent was obtained from all the patients.

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 that occurred during the study. 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. The first three authors wrote the first draft of the manuscript, and all the steering committee members contributed to subsequent versions, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Patients

Patients were eligible for inclusion in the study if they were 18 years of age or older; had objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism; had been treated for 6 to 12 months with an anticoagulant agent, including a vitamin K antagonist or a direct oral anticoagulant agent such as dabigatran, rivaroxaban, apixaban, or edoxaban; and had not interrupted therapy for more than 7 days before randomization.

Patients were ineligible if they had a contraindication to continued anticoagulant therapy or

if they required extended anticoagulant therapy at therapeutic doses or antiplatelet therapy. Additional ineligibility criteria included a calculated creatinine clearance of less than 30 ml per minute[23,24] or hepatic disease associated with a coagulopathy. A full list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

Randomization with a block size of six was performed with the use of an interactive voice-response system and was stratified according to the index diagnosis (deep-vein thrombosis or pulmonary embolism) and country. Patients were enrolled at least 24 hours after they had received the last dose of a direct oral anticoagulant agent or, if they were receiving a vitamin K antagonist, when the international normalized ratio was 2.5 or lower. Patients were assigned, in a 1:1:1 ratio, to receive 20 mg of rivaroxaban, 10 mg of rivaroxaban, or 100 mg of aspirin, all given once daily with food. Rivaroxaban (20 mg and 10 mg) and matching placebo were provided as identical-appearing, immediate-release film-coated tablets, whereas aspirin and matching placebo were provided as enteric-coated tablets. The intended duration of administration of the study drug was 12 months, but patients who underwent randomization after the requisite number of primary efficacy outcomes had been reached were treated for at least 6 months.

OUTCOME MEASURES

The primary efficacy outcome was a composite of symptomatic, recurrent fatal or nonfatal venous thromboembolism and unexplained death for which pulmonary embolism could not be ruled out. Recurrent venous thromboembolism included fatal and nonfatal pulmonary embolism and deep-vein thrombosis. Other efficacy outcomes were myocardial infarction, ischemic stroke, systemic embolism, venous thrombosis in locations other than the deep veins of the lower limbs, and death from any cause. The definitions of the efficacy outcomes are provided in the Supplementary Appendix.

The principal safety outcome was major bleeding.[25] Other safety outcomes were clinically relevant nonmajor bleeding, a composite of major or clinically relevant nonmajor bleeding, and nonmajor bleeding that led to study-drug interruption for more than 14 days.[12,13] 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. Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but 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 living.[26] (Further details regarding the criteria are provided in the Supplementary Appendix.)

SURVEILLANCE AND FOLLOW-UP

Patients underwent assessment, either in the clinic or by telephone, at days 30, 90, 180, 270, and 360 and at 30 days after stopping the study medication. All the patients who stopped a study treatment earlier than scheduled were followed until 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.[22] Continuation of anticoagulant or antiplatelet therapy after study completion was at the discretion of the treating physician.

STATISTICAL ANALYSIS

The study was designed to test the hypothesis that each dose of rivaroxaban would be superior to aspirin with respect to the primary efficacy outcome. We determined that the occurrence of 80 primary efficacy outcome events would provide a power of 90% to show the superiority of each dose of rivaroxaban over aspirin (each at a two-sided alpha level of 0.05), assuming a relative risk reduction of 70% with 20 mg of rivaroxaban and of 60% with 10 mg of rivaroxaban.[7] On the basis of an expected frequency of the primary efficacy outcome of 5.0% at 12 months with aspirin,[12,13] we calculated that we would need to enroll 2850 patients. However, this number was increased to 3300 when review of blinded data revealed a lower-than-expected overall incidence of the primary efficacy outcome.

The efficacy and safety analyses included all the patients who had undergone randomization with valid informed consent and who had received at least one dose of a study medication

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

Characteristic	Rivaroxaban		Aspirin
	20 mg (N=1107)	10 mg (N=1127)	100 mg (N=1131)
Male sex — no. (%)	602 (54.4)	620 (55.0)	643 (56.9)
Age — yr			
Mean ±SD	57.9±14.7	58.8±14.7	58.8±14.7
Median (IQR)	59.0 (48.0–69.0)	60.0 (48.0–69.0)	60.0 (48.0–69.0)
Weight — no. (%)			
<70 kg	276 (24.9)	283 (25.1)	277 (24.5)
70 to ≤90 kg	471 (42.5)	480 (42.6)	508 (44.9)
>90 kg	360 (32.5)	364 (32.3)	346 (30.6)
Body-mass index†			
<30	712 (64.3)	751 (66.6)	756 (66.8)
≥30	394 (35.6)	376 (33.4)	375 (33.2)
Missing data	1 (0.1)	0	0
Creatinine clearance — no. (%)			
<30 ml/min	1 (0.1)	2 (0.2)	1 (0.1)
30 to <50 ml/min	40 (3.6)	49 (4.3)	63 (5.6)
50 to <80 ml/min	279 (25.2)	302 (26.8)	277 (24.5)
≥80 ml/min	787 (71.1)	774 (68.7)	790 (69.8)
Index event — no. (%)			
Isolated deep-vein thrombosis	565 (51.0)	565 (50.1)	577 (51.0)
Isolated pulmonary embolism	381 (34.4)	381 (33.8)	366 (32.4)
Both deep-vein thrombosis and pulmonary embolism	155 (14.0)	179 (15.9)	181 (16.0)
Index event asymptomatic or unconfirmed	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index venous thromboembolism — no. (%)			
Provoked	666 (60.2)	647 (57.4)	663 (58.6)
Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
Hormonal therapy — no. (%)			
Estrogens	8 (0.7)	6 (0.5)	8 (0.7)
Progestins	29 (2.6)	30 (2.7)	30 (2.7)
Known thrombophilia — no. (%)	79 (7.1)	74 (6.6)	70 (6.2)
Previous venous thromboembolism — no. (%)	198 (17.9)	197 (17.5)	194 (17.2)
Active cancer — no. (%)	25 (2.3)	27 (2.4)	37 (3.3)
Median duration of study-drug administration (IQR) — days	349 (189–362)	353 (190–362)	350 (186–362)
Individual intended study duration — no. (%)			
6 mo	206 (18.6)	209 (18.5)	212 (18.7)
9 to <12 mo	229 (20.7)	240 (21.3)	238 (21.0)
12 mo	672 (60.7)	678 (60.2)	681 (60.2)

* There were no significant differences in the baseline characteristics among the groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

(intention-to-treat population). The per-protocol population excluded patients who had a rate of adherence to the study-drug regimen of less than 80% or who had other major protocol violations. Efficacy outcomes were considered during the individual intended treatment period, whereas safety outcomes were considered during the time from administration of the first dose of a study drug to 48 hours after the administration of the last dose. Efficacy and safety outcomes were analyzed with the use of a Cox proportional-hazards model, stratified according to the index diagnosis (deep-vein thrombosis or pulmonary embolism). Kaplan–Meier curves were constructed to display the distribution of events over time.

RESULTS

STUDY PATIENTS

From March 2014 through March 2016, a total of 3396 patients from 244 sites in 31 countries were enrolled. After the exclusion of 31 patients (0.9%) because they did not receive any study drug, 3365 patients were included in the primary analyses. The characteristics of patients in the three study groups were similar at baseline, as was the median duration of study treatment (Table 1). Figure 1 shows the random assignment and follow-up of the patients.

EFFICACY

A primary efficacy outcome event occurred in 17 of 1107 patients (1.5%) who were receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) who were receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) who were receiving aspirin. Fatal venous thromboembolism occurred in 2 patients (0.2%) who were receiving 20 mg of rivaroxaban, in no patients who were receiving 10 mg of rivaroxaban, and in 2 patients (0.2%) who were receiving aspirin (Table 2). Both rivaroxaban doses were superior to aspirin

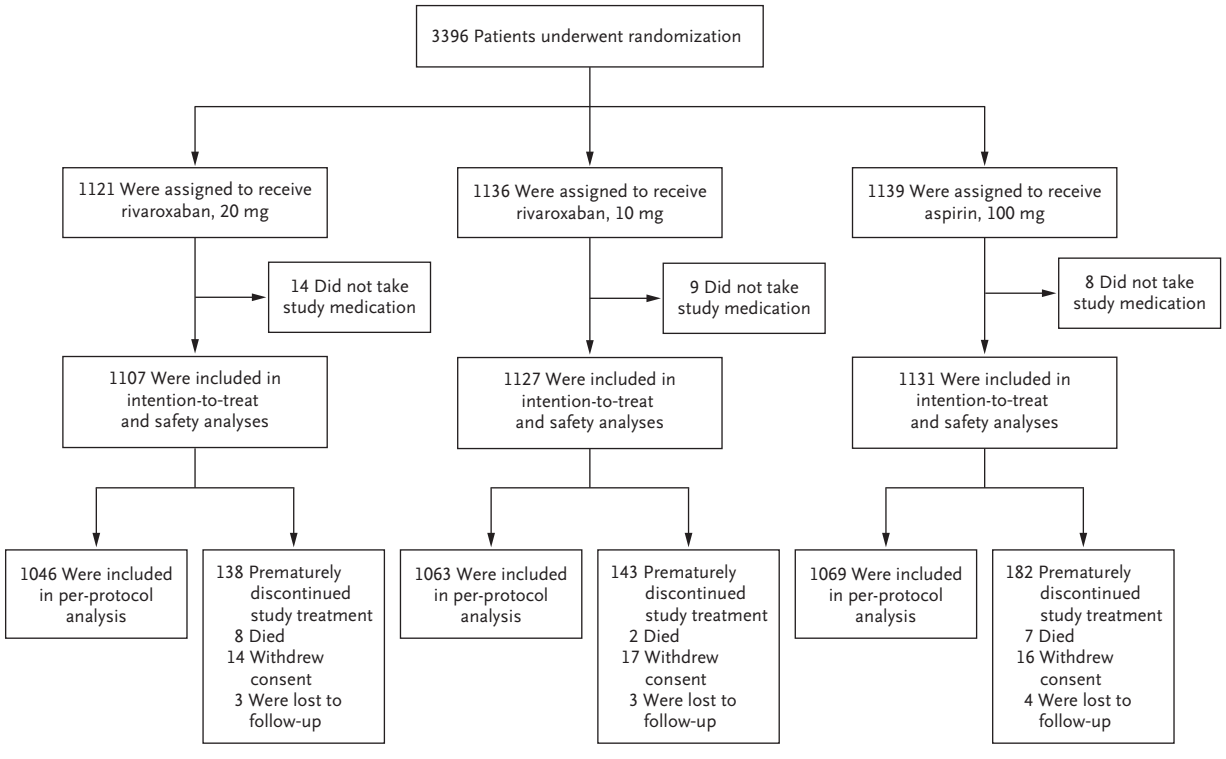


Figure 1. Enrollment and Outcomes.

The intention-to-treat population included all the patients who had undergone randomization with valid informed consent and who had received at least one dose of a study medication. The per-protocol population included all those in the intention-to-treat population with the exception of those who had a rate of adherence to the study-drug regimen of less than 80% or who had other major protocol violations. The main reasons for premature discontinuation of a study medication were adverse events, nonadherence to the study-drug regimen, protocol violations, and efficacy or safety outcomes.

Table 2. Prespecified Efficacy Outcomes.*

Outcome	Rivaroxaban		Aspirin	Rivaroxaban, 20 mg, vs. Aspirin	Rivaroxaban, 10 mg, vs. Aspirin	Rivaroxaban, 20 mg vs. 10 mg	
	20 mg (N=1107)	10 mg (N=1127)	100 mg (N=1131)	Hazard Ratio (95% CI)†	Hazard Ratio (95% CI)†	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary efficacy outcome							
Recurrent venous thromboembolism	17 (1.5)	13 (1.2)	50 (4.4)	0.34 (0.20–0.59)	0.26 (0.14–0.47)	1.34 (0.65–2.75)	0.42
Deep-vein thrombosis	9 (0.8)	7 (0.6)	29 (2.6)				
Pulmonary embolism	6 (0.5)	5 (0.4)	19 (1.7)				
Deep-vein thrombosis and pulmonary embolism	0	1 (0.1)	0				
Fatal venous thromboembolism	2 (0.2)	0	2 (0.2)				
Deep-vein thrombosis as index event							
Deep-vein thrombosis	4 (0.4)	4 (0.4)	22 (1.9)				
Pulmonary embolism	0	1 (0.1)	5 (0.4)				
Fatal venous thromboembolism	1 (0.1)	0	0				
Pulmonary embolism as index event							
Deep-vein thrombosis	5 (0.5)	3 (0.3)	7 (0.6)				
Pulmonary embolism	6 (0.5)	4 (0.4)	14 (1.2)				
Deep vein thrombosis and pulmonary embolism	0	1 (0.1)	0				
Fatal venous thromboembolism	1 (0.1)	0	2 (0.2)				
Other efficacy outcomes							
Primary efficacy outcome, myocardial infarction, ischemic stroke, or systemic embolism	19 (1.7)	18 (1.6)	56 (5.0)	0.34 (0.20–0.57)	0.32 (0.19–0.54)	1.08 (0.57–2.06)	0.80
Myocardial infarction	1 (0.1)	0	4 (0.4)				
Ischemic stroke	2 (0.2)	4 (0.4)	2 (0.2)				
Systemic embolism	0	1 (0.1)	1 (0.1)				
Death from any cause	8 (0.7)	2 (0.2)	7 (0.6)				
Bleeding	1 (0.1)	0	1 (0.1)				
Pulmonary embolism or unexplained death and pulmonary embolism not ruled out	2 (0.2)	0	2 (0.2)				
Cancer	1 (0.1)	2 (0.2)	3 (0.3)				

Infectious disease	2 (0.2)	0	0			
Heart failure	0	0	1 (0.1)			
Other respiratory failure	2 (0.2)	0	0			
Primary efficacy outcome or death from any cause	23 (2.1)	15 (1.3)	55 (4.9)	0.42 (0.26–0.68)	0.27 (0.15–0.47)	1.57 (0.82–3.00)	0.18
Primary efficacy outcome or venous thrombosis in other location	20 (1.8)	16 (1.4)	57 (5.0)	0.35 (0.21–0.58)	0.28 (0.16–0.48)	1.28 (0.66–2.46)	0.81
Superficial-vein thrombosis	4 (0.4)	1 (0.1)	6 (0.5)				
Upper-limb thrombosis	0	1 (0.1)	1 (0.1)				
Ophthalmic-vein thrombosis	0	1 (0.1)	0				
Primary efficacy outcome, myocardial infarction, ischemic stroke, systemic embolism, or venous thrombosis in other location	22 (2.0)	21 (1.9)	63 (5.6)	0.35 (0.22–0.57)	0.33 (0.20–0.54)	1.07 (0.59–1.95)	0.81

* Efficacy outcomes were assessed in all the patients who had undergone randomization and received at least one dose of a study drug (intention-to-treat population).
† P<0.001 for all the comparisons between the 10-mg and 20-mg doses of rivaroxaban and aspirin.

with respect to the primary efficacy outcome (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). The hazard ratio for the comparison between the 20-mg and 10-mg rivaroxaban regimens was 1.34 (95% CI, 0.65 to 2.75; P=0.42). Similar results were found for the other efficacy outcomes (Table 2, and Table S4 in the Supplementary Appendix).

With aspirin, the rate of recurrent venous thromboembolism was 3.6% among the patients in whom the index event was provoked (i.e., associated with a known event, such as surgery or hospital admission) and 5.6% among those in whom the index event was unprovoked (i.e., idiopathic) (Table 3). Rates of recurrence in patients whose index events were provoked or unprovoked were lower in both the 20-mg rivaroxaban group (1.4% and 1.8%, respectively) and the 10-mg rivaroxaban group (0.9% and 1.5%, respectively) than in the aspirin group. Figure 2A shows the time course of symptomatic fatal or nonfatal recurrent venous thromboembolism. Of the 31 patients who were excluded from the analyses because they did not take any study drug, 1 patient who was assigned to receive 20 mg of rivaroxaban had a nonfatal primary efficacy outcome event.

SAFETY

Major bleeding occurred in 6 patients (0.5%) in the 20-mg rivaroxaban group and in 5 patients (0.4%) in the 10-mg rivaroxaban group, as compared with 3 patients (0.3%) in the aspirin group (Table 4). Figure 2B shows the time course of major bleeding episodes.

Clinically relevant nonmajor bleeding occurred in 30 patients (2.7%) in the 20-mg rivaroxaban group and in 22 patients (2.0%) in the 10-mg rivaroxaban group, as compared with 20 patients (1.8%) in the aspirin group (Table 4). Similar results were found for the composite outcome of major or clinically relevant nonmajor bleeding. Nonmajor bleeding that was associated with a study-drug interruption for more than 14 days occurred in 17 patients (1.5%) in the 20-mg rivaroxaban group and in 12 patients (1.1%) in the 10-mg rivaroxaban group, as compared with 12 patients (1.1%) in the aspirin group.

Table 3. Rates of Recurrent Venous Thromboembolism and Major Bleeding, According to Risk Profile and Duration of Anticoagulation before Randomization.*

Variable	Rivaroxaban, 20 mg (N=1107)		Rivaroxaban, 10 mg (N=1127)		Aspirin, 100 mg (N=1131)	
	Recurrent VTE	Major Bleeding	Recurrent VTE	Major Bleeding	Recurrent VTE	Major Bleeding
	number/total number (percent)					
Risk profile						
Provoked index event	9/666 (1.4)	2/666 (0.3)	6/647 (0.9)	3/647 (0.5)	24/663 (3.6)	2/663 (0.3)
Unprovoked index event	8/441 (1.8)	4/441 (0.9)	7/480 (1.5)	2/480 (0.4)	26/468 (5.6)	1/468 (0.2)
History of venous thromboembolism						
Yes	3/198 (1.5)	2/198 (1.0)	2/197 (1.0)	0/197	17/194 (8.8)	1/194 (0.5)
No	14/909 (1.5)	4/909 (0.4)	11/930 (1.2)	5/930 (0.5)	33/937 (3.5)	2/937 (0.2)
Duration of anticoagulation before randomization						
<9 mo	12/774 (1.6)	3/774 (0.4)	7/782 (0.9)	3/782 (0.4)	35/793 (4.4)	3/793 (0.4)
≥9 mo	5/333 (1.5)	3/333 (0.9)	6/345 (1.7)	2/345 (0.6)	15/338 (4.4)	0/338

* Recurrent venous thromboembolism (VTE) was assessed in the intention-to-treat population. Major bleeding was assessed in the same population but during the period of study-drug administration plus a window of 2 days.

OTHER OUTCOMES

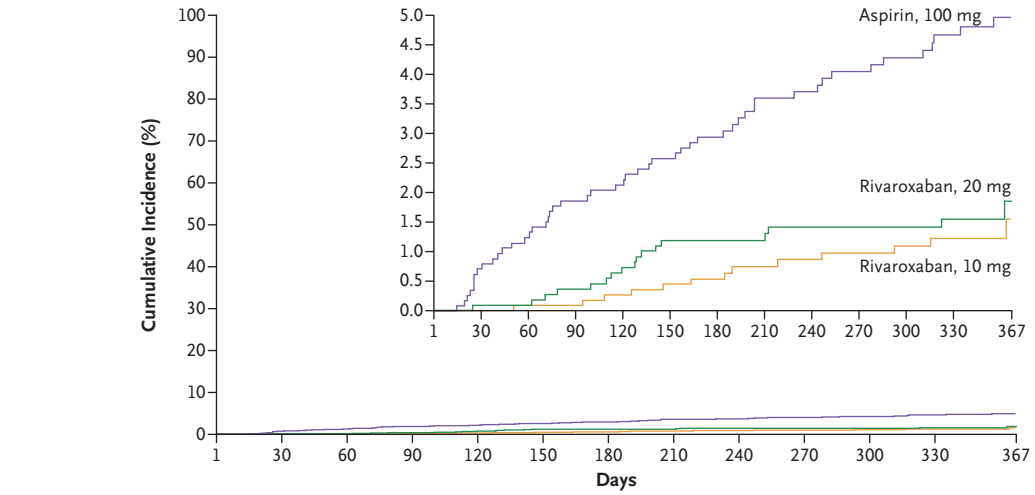
Myocardial infarction, stroke, or systemic embolism occurred in 3 patients (0.3%) in the 20-mg rivaroxaban group, in 5 patients (0.4%) in the 10-mg rivaroxaban group, and in 7 patients (0.6%) in the aspirin group (Table 2). The rates of death from any cause were 0.7% and 0.2% in the 20-mg and 10-mg rivaroxaban groups, respectively, as compared with 0.6% in the aspirin group. Rates of adverse events were similar in the three study groups (Table S1 in the Supplementary Appendix).

In prespecified subgroup analyses of the primary efficacy outcome and the composite outcome of major and clinically relevant nonmajor bleeding, results were consistent with the overall treatment effects (Figs. S1 through S4 in the Supplementary Appendix). During the 30-day follow-up after the end of the active study period, symptomatic recurrent venous thromboembolism occurred in 2 patients (0.2%) in the 20-mg rivaroxaban group, in 4 patients (0.4%) in the 10-mg rivaroxaban group, and in 6 patients (0.6%) in the aspirin group.

DISCUSSION

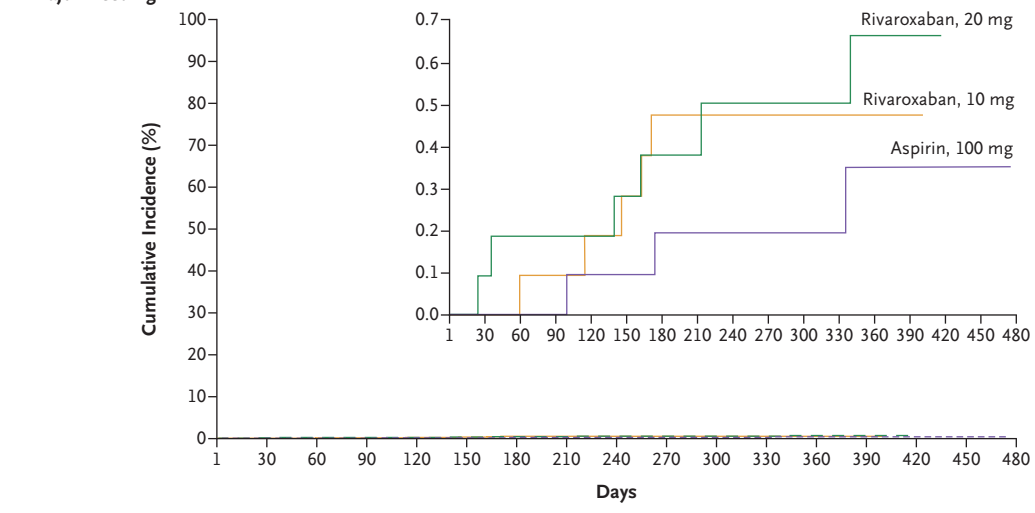
Clinical strategies for extended anticoagulation in patients with venous thromboembolism are uncertain. Previous studies have shown that as compared with placebo, aspirin reduced the relative risk of recurrent venous thromboembolism by 32% (2.4 percentage points),[12,13] whereas a 20-mg dose of rivaroxaban reduced the relative risk by 82% (6.8 percentage points).[7] Consistent with those findings, our study shows that as compared with aspirin, both the 20-mg and 10-mg doses of rivaroxaban reduced the relative risk of recurrent venous thromboembolism by about 70% (approximately 3 percentage points). These benefits were observed with rates of major and clinically relevant nonmajor bleeding that were low and similar to those with aspirin. Therefore, we found that rivaroxaban was more effective than aspirin for the prevention of recurrent venous thromboembolism and was associated with a similar risk of bleeding.

What are the clinical implications of these findings? This study included patients with both



No. at Risk

Rivaroxaban, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0



No. at Risk

Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Figure 2. Kaplan–Meier Rates of Recurrent Fatal or Nonfatal Venous Thromboembolism and Major Bleeding.

Kaplan–Meier curves are shown for the first event of recurrent fatal or nonfatal venous thromboembolism during the individual intended treatment periods (Panel A) and for the first episode of major bleeding during the period between the administration of the first dose of a study drug and 48 hours after the administration of the last dose (Panel B). In each panel, the inset shows the same data on an enlarged y axis.

Table 4. Prespecified Safety Outcomes.*

Outcome	Rivaroxaban		Aspirin	Rivaroxaban, 20 mg, vs. Aspirin		Rivaroxaban, 10 mg, vs. Aspirin		Rivaroxaban, 20 mg vs. 10 mg	
	20 mg (N=1107)	10 mg (N=1127)	100 mg (N=1131)	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)								
Principal safety outcome									
Major bleeding†	6 (0.5)	5 (0.4)	3 (0.3)	2.01 (0.50–8.04)	0.32	1.64 (0.39–6.84)	0.50	1.23 (0.37–4.03)	0.74
Fatal	1 (0.1)	0	1 (0.1)						
Intracranial	0	0	1 (0.1)						
Pericardial	1 (0.1)	0	0						
Nonfatal bleeding in a critical site	4 (0.4)	2 (0.2)	1 (0.1)						
Intracranial	3 (0.3)	1 (0.1)	1 (0.1)						
Pulmonary	1 (0.1)	0	0						
Intramuscular	0	1 (0.1)	0						
Nonfatal, noncritical bleeding with decrease in hemoglobin of ≥2 g/dl or transfusion of ≥2 units	1 (0.1)	3 (0.3)	1 (0.1)						
Gastrointestinal	1 (0.1)	2 (0.2)	1 (0.1)						
Abdominal	0	1 (0.1)	0						
Other safety outcomes									
Major or clinically relevant nonmajor bleeding†	36 (3.3)	27 (2.4)	23 (2.0)	1.59 (0.94–2.69)	0.08	1.16 (0.67–2.03)	0.60	1.37 (0.83–2.26)	0.21
Clinically relevant nonmajor bleeding†	30 (2.7)	22 (2.0)	20 (1.8)	1.53 (0.87–2.69)	0.14	1.09 (0.59–2.00)	0.78	1.40 (0.81–2.43)	0.23
Minor bleeding†	160 (14.5)	133 (11.8)	122 (10.8)						
Nonmajor bleeding associated with study drug interruption for >14 days	17 (1.5)	12 (1.1)	12 (1.1)	1.44 (0.69–3.02)	0.33	0.99 (0.44–2.20)	0.96	1.46 (0.70–3.06)	0.31

* Safety outcomes were assessed in the intention-to-treat population during the period of study-drug administration plus a 2-day window.
† Bleeding episodes were defined according to the criteria of the International Society on Thrombosis and Haemostasis.

provoked and unprovoked venous thromboembolism for whom there was equipoise regarding the need for continued anticoagulation. Patients with unprovoked venous thromboembolism are known to be at high risk for recurrence, but the risk of recurrence among those in whom venous thromboembolism was provoked by minor transient or persistent risk factors is less certain. We found that patients with venous thromboembolism with ongoing risk factors have an appreciable risk of recurrence because even with aspirin, the rate of recurrent venous thromboembolism in such patients was 3.6%, as compared with a rate of recurrence of 5.6% in those with unprovoked venous thromboembolism. Rivaroxaban reduced the relative risk of recurrence by about 70% in patients with both unprovoked and provoked venous thromboembolism. Consequently, the number of patients who would need to be treated for up to 12 months with rivaroxaban instead of aspirin to prevent one episode of fatal or nonfatal recurrent venous thromboembolism without increasing the risk of bleeding was 33 with the 20-mg dose and 30 with the 10-mg dose. Prevention of recurrent pulmonary embolism is particularly important, because the case-fatality rate at 30 days is at least twice as high with pulmonary embolism as with deep-vein thrombosis.[27]

Our study has several potential limitations. First, patients who required extended treatment with therapeutic doses of anticoagulant agents were excluded. Therefore, it remains unknown whether the 10-mg dose of rivaroxaban would be sufficient to prevent recurrence in such patients. Second, in this study and in the previous trial comparing rivaroxaban with placebo for extended treatment of venous thromboembolism, therapy was given for up to 12 months. Consequently, additional studies are needed to determine the utility of continuing treatment for longer periods. Third, our study was not powered to show the noninferiority of the 10-mg dose of rivaroxaban to the established treatment regimen of 20 mg, so any conclusions with respect to this issue are speculative.

In conclusion, we found that rivaroxaban, at both a treatment dose (20 mg) and a thromboprophylactic dose (10 mg), was more effective than aspirin for the prevention of recurrent venous thromboembolism among patients who were in equipoise for continued anticoagulation. The lower risk of a recurrent event among the patients who received rivaroxaban was associated with a rate of bleeding similar to that with aspirin.

Supported by Bayer Pharmaceuticals.

Dr. Weitz reports receiving consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Ionis Pharmaceuticals, Janssen, Merck, Novartis, Portola, and Pfizer; Drs. Lensing, Freitas, Holberg, Pap, and Berkowitz, being employees of Bayer; Dr. Prins, receiving consulting fees from Pfizer and Daiichi Sankyo; Dr. Bauersachs, receiving consulting and lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo; Dr. Beyer-Westendorf, receiving grant support, lecture fees, and fees for serving on advisory boards from Boehringer Ingelheim, Daiichi Sankyo, and Pfizer; Dr. Bounameaux, receiving grant support and fees for serving on the Thrombosis Research Institute Garfield Registry steering committee, fees for serving on the Bayer EINSTEIN CHOICE Study steering committee, consulting fees from Amgen, and fees for serving on advisory boards from Bayer, Pfizer, and Sanofi Aventis; Dr. Brighton, receiving lecture fees from Bayer, Novo Nordisk, and GlaxoSmithKline; Dr. Cohen, receiving fees for serving on a committee for Boehringer Ingelheim, grant support and fees for serving on committees from Bristol-Myers Squibb and Daiichi Sankyo, consulting fees and fees for serving on steering committees from Johnson & Johnson and Portola, grant support, consulting fees, and fees for serving on committees from Pfizer, and consulting fees from Sanofi, Janssen, and Ono Pharmaceuticals; Dr. Davidson, receiving consulting fees from Janssen and Portola; Dr. Decousus, receiving fees for attending symposia from Aspen, fees for serving on advisory boards from Pfizer and Bristol-Myers Squibb, and grant support and fees for board membership from Daiichi Sankyo and Bayer; Dr. Kakkar, receiving grant support, consulting fees, and lecture fees from Bayer and consulting and lecture fees from Sanofi, Janssen, Boehringer Ingelheim, and Daiichi Sankyo; Dr. Haskell, being an employee of Johnson & Johnson; Dr. van Bellen, receiving lecture fees and fees for serving on an advisory board from Bayer and Daiichi Sankyo and for serving on an advisory board from Bristol-Myers Squibb; Dr. Verhamme, receiving grant support, lecture fees, and fees for serving on an advisory board from Boehringer Ingelheim and LEO Pharma, lecture fees from Pfizer and Bristol-Myers Squibb, grant support from Sanofi, lecture fees and fees for serving on an advisory board from Daiichi Sankyo, and fees for serving on an advisory board from Portola Pharmaceuticals; Dr. Wells, receiving grant support, lecture fees, and fees for serving on an advisory board from Bayer, fees for serving on a writing committee from Itreas, consulting fees from Janssen Scientific Affairs, grant support from Bristol-Myers Squibb and Pfizer, and lecture fees from Daiichi Sankyo; and Dr. Prandoni, receiving consulting and lecture fees from Bayer, Sanofi, Daiichi Sankyo, 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.

APPENDIX

The authors' full names and academic degrees are as follows: Jeffrey I. Weitz, M.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., Rupert Bauersachs, M.D., Jan Beyer-Westendorf, M.D., Henri Bounameaux, M.D., Timothy A. Brighton, M.D., Alexander T. Cohen, M.D., Bruce L. Davidson, M.D., M.P.H., Hervé Decousus, M.D., Maria C.S. Freitas, M.D., Ph.D., Gerlind Holberg, V.D.,

Ph.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Lloyd Haskell, M.D., Bonno van Bellen, M.D., Akos F. Pap, M.Sc., Scott D. Berkowitz, M.D., Peter Verhamme, M.D., Philip S. Wells, M.D., and Paolo Prandoni, M.D., Ph.D.

The authors' affiliations are as follows: the Thrombosis and Atherosclerosis Research Institute and McMaster University, Hamilton, ON (J.I.W.), and the Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Ottawa (P.S.W.) — both in Canada; Bayer Pharmaceuticals, Leverkusen (A.W.A.L., M.C.S.F., G.H., A.F.P., S.D.B.), Vascular Medicine, Klinikum Darmstadt, Darmstadt (R.B.), the Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz (R.B.), and the Department of Hematology, Medical Clinic I, University Hospital Carl Gustav Carus, Dresden (J.B.-W.) — all in Germany; the Department of Epidemiology and Technology Assessment, University of Maastricht, Maastricht, the Netherlands (M.H.P.); the Division of Angiology and Hemostasis and the Faculty of Medicine, University of Geneva, Geneva (H.B.); the Department of Haematology, Prince of Wales Hospital, Sydney (T.A.B.); the Department of Haematology and Oncology, King's College London (J.B.-W.), the Department of Haematological Medicine, Guy's and St. Thomas' Hospitals, King's College Hospital (A.T.C.), and Thrombosis Research Institute and University College London (A.K.K.) — all in London; the University of Washington School of Medicine, Seattle (B.L.D.); Centre d'Investigation Clinique 1408, Sainbiose U1059, Investigation Network on Venous Thromboembolism, Service de Médecine Vasculaire et Thérapeutique, Centre Hospitalo-Universitaire, Hôpital Nord, Saint Etienne, France (H.D.); Janssen Research and Development, Raritan, NJ (L.H.); Hospital Beneficência Portuguesa, São Paulo (B.B.); Vascular Medicine and Hemostasis, University of Leuven, Leuven, Belgium (P.V.); and the Department of Cardiothoracic and Vascular Sciences, Vascular Medicine Unit, University of Padua, Padua, Italy (P.P.).

REFERENCES

1. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. Thromb Res 2014;134:931-8.
2. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756-64.
3. Venous thromboembolism in adult hospitalizations — United States, 2007–2009. MMWR Morb Mortal Wkly Rep 2012;61:401-4.
4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-52.
5. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
6. 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.
7. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
8. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.
9. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.
10. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362:523-6.
11. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003;348:1435-41.
12. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-87.
13. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959-67.
14. 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.
15. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
16. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
17. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11:21.
18. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.
19. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372:31-9.
20. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.
21. Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009;373:1673-80.
22. Weitz JI, Bauersachs R, Beyer-Westendorf J, et al. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism: rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost 2015;114:645-50.
23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
25. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
26. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119-26.
27. Spencer FA, Gore JM, Lessard D, Douketis JD, Emery C, Goldberg RJ. Patient outcomes after deep vein thrombosis and pulmonary embolism: the Worcester Venous Thromboembolism Study. Arch Intern Med 2008;168:425-30.