ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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This article (10.1056/NEJMoa1007903) was published on December 4, 2010, and updated December 8, 2010, at NEJM.org.

N Engl J Med 2010;363:2499-510.

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

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

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

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

METHODS

STUDY DESIGN AND OVERSIGHT

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

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

PATIENTS

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

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

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

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

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

TREATMENT REGIMENS

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

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

SURVEILLANCE AND FOLLOW-UP

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

OUTCOME ASSESSMENTS

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

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

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

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

STATISTICAL ANALYSIS

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

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

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

RESULTS

STUDY PATIENTS

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

TREATMENT AND FOLLOW-UP

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

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

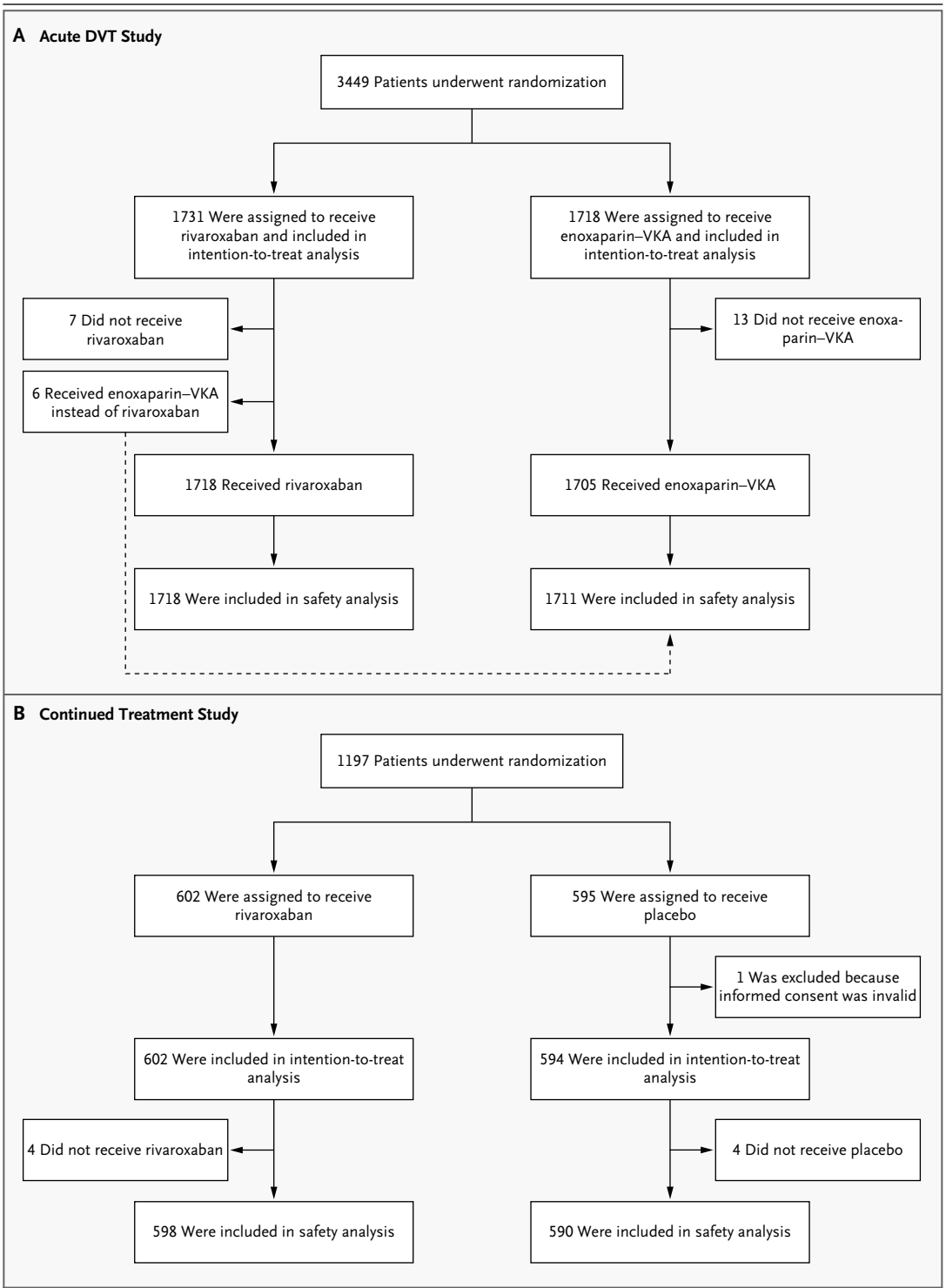

Figure 1. Numbers of Patients Who Underwent Randomization, Received the Study Drugs, and Were Included in the Efficacy and Safety Analyses in the Acute DVT and Continued Treatment Studies.

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

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

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

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

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

CLINICAL OUTCOMES IN THE ACUTE DVT STUDY

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

Table 2. Characteristics of Treatment in Each Study.*

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

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

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

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

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

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

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

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

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

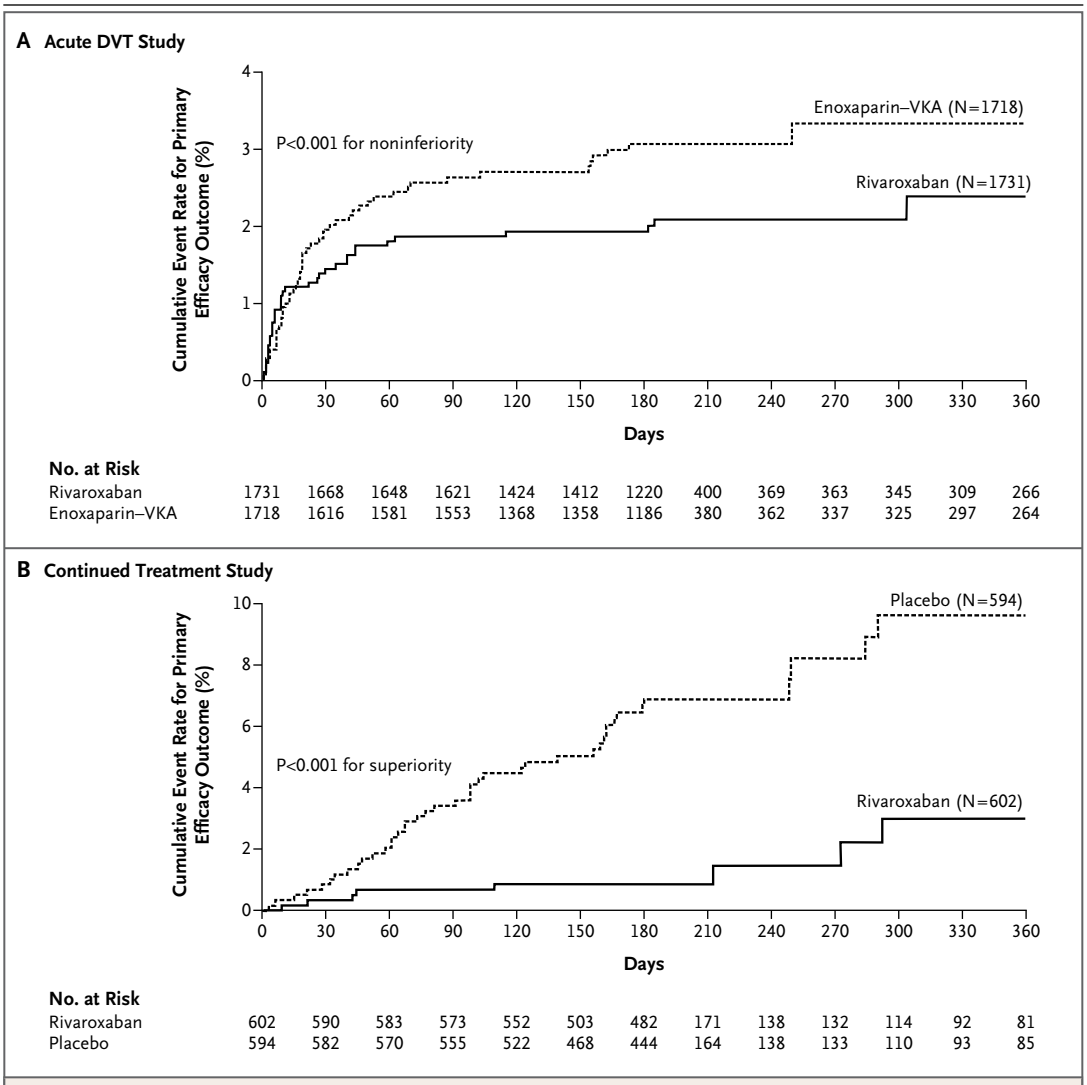

Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.
VKA denotes vitamin K antagonist.

CLINICAL OUTCOMES IN THE CONTINUED TREATMENT STUDY

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

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

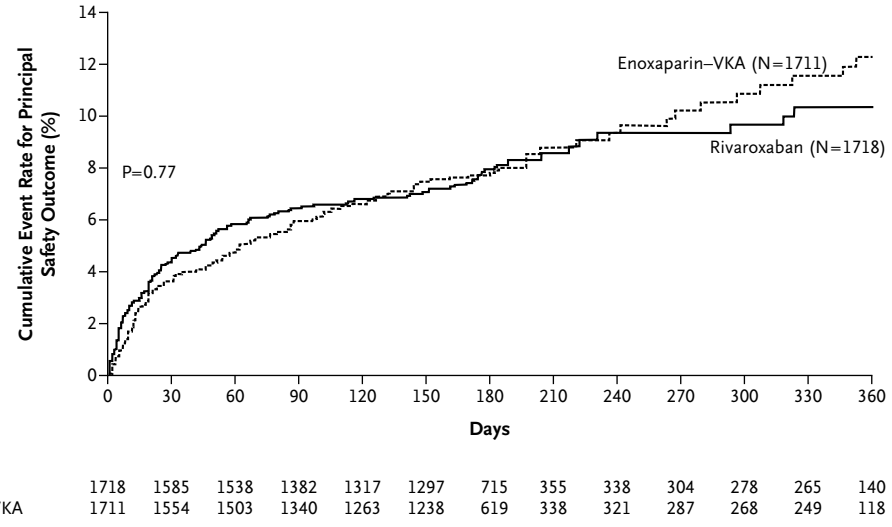

Figure 3. Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome in the Acute DVT Study.
VKA denotes vitamin K antagonist.

DISCUSSION

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

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

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

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

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

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

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

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

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

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

Supported by Bayer Schering Pharma and Ortho-McNeil.

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

APPENDIX

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