ORIGINAL ARTICLE

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

ABSTRACT

BACKGROUND

A fixed-dose regimen of rivaroxaban, an oral factor Xa inhibitor, has been shown to be as effective as standard anticoagulant therapy for the treatment of deep-vein thrombosis, without the need for laboratory monitoring. This approach may also simplify the treatment of pulmonary embolism.

METHODS

In a randomized, open-label, event-driven, noninferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, we compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS

Rivaroxaban was noninferior to standard therapy (noninferiority margin, 2.0; P=0.003) for the primary efficacy outcome, with 50 events in the rivaroxaban group (2.1%) versus 44 events in the standard-therapy group (1.8%) (hazard ratio, 1.12; 95% confidence interval [CI], 0.75 to 1.68). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group (hazard ratio, 0.90; 95% CI, 0.76 to 1.07; P=0.23). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P=0.003). Rates of other adverse events were similar in the two groups.

CONCLUSIONS

A fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit–risk profile. (Funded by Bayer HealthCare and Janssen Pharmaceuticals; EINSTEIN-PE ClinicalTrials.gov number, NCT00439777.)

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Pulmonary embolism is a common disease, with an estimated annual incidence of 70 cases per 100,000 population.[1,2] The condition usually leads to hospitalization and may recur; it can be fatal.[3]

For half a century, the standard therapy for most patients with pulmonary embolism has been the administration of heparin, overlapped and followed by a vitamin K antagonist.[4,5] This regimen is effective but complex.[5-9] Recently developed oral anticoagulants that are directed against factor Xa or thrombin overcome some limitations of standard therapy, including the need for injection and for regular dose adjustments on the basis of laboratory monitoring.[5,10,11]

Current data suggest that rivaroxaban, an oral direct inhibitor of factor Xa, is effective and safe for the prevention of venous thromboembolism after major orthopedic surgery, for the prevention of stroke in patients with atrial fibrillation, and in the treatment of acute coronary syndromes.[12-14] The EINSTEIN program evaluated the concept of using rivaroxaban alone for anticoagulant therapy for acute deep-vein thrombosis and pulmonary embolism, replacing both heparin and vitamin K antagonists.[15,16] This single-drug approach, starting with an increased dose for 3 weeks, appeared to be successful in treating deep-vein thrombosis. Here we report the findings for this regimen in patients with pulmonary embolism.

Methods

Study Design and Organization

The EINSTEIN–PE study was a randomized, open-label trial of the efficacy and safety of rivaroxaban as compared with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis. The trial was sponsored by Bayer HealthCare and Janssen Pharmaceuticals.

The steering committee had final responsibility for the study design, clinical protocol, study oversight, data verification, and analyses. The protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review board at each center, and written informed consent was obtained from all patients. The trial sponsor collected and maintained all the data. A central committee whose members were unaware of the study-group assignments adjudicated the results of all baseline lung-imaging tests and all suspected outcome events. An independent data and safety monitoring board periodically reviewed the study outcomes. The writing committee wrote the manuscript, made the decision to submit the manuscript for publication, and vouches for the accuracy and completeness of the data as well as the fidelity of this report to the study protocol.

Patients

Patients were eligible if they were of legal age and had an acute, symptomatic pulmonary embolism with objective confirmation, with or without symptomatic deep-vein thrombosis. Patients were ineligible if they had received a therapeutic dose 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 thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for treatment of the current episode; or if they had any contraindication listed in the local labeling of enoxaparin, warfarin, or acenocoumarol. Other criteria for ineligibility 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 more than three times the upper limit of the normal range; bacterial endocarditis; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment; a systolic blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breast-feeding; concomitant use of a strong inhibitor of cytochrome P-450 3A4 (CYP3A4) (e.g., a protease inhibitor for human immunodeficiency virus infection or systemic ketoconazole) or a CYP3A4 inducer (e.g., rifampin, carbamazepine, or phenytoin); participation in another experimental pharmacotherapeutic program within 30 days; or a life expectancy of less than 3 months.

Randomization and Treatment Regimens

Randomization was performed with the use of a computerized voice-response system and was stratified according to country and the intended treatment duration (3, 6, or 12 months). The intended

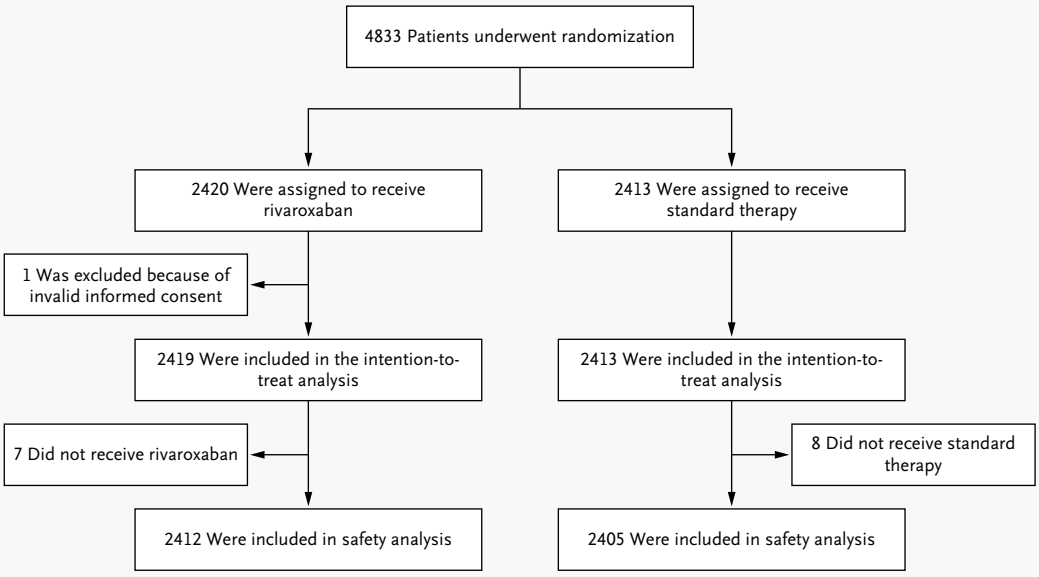


Figure 1. Enrollment and Outcomes.

duration of treatment was determined by the treating physician before randomization.

Patients who were assigned to the rivaroxaban group were given 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily. Patients who were assigned to the standard-therapy group received enoxaparin at a dose of 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 a month.

The use of nonsteroidal antiinflammatory drugs and antiplatelet agents was discouraged. Aspirin administered at a dose of no more than 100 mg per day, clopidogrel at a dose of 75 mg per day, or both were allowed.

SURVEILLANCE AND FOLLOW-UP

We followed the patients for the intended treatment period and assessed them at fixed intervals that were identical in the two study groups, using a checklist 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 symptoms or signs occurred. In the case of suspected venous thromboembolism, the protocol required objective testing.

OUTCOME ASSESSMENT

The primary efficacy outcome was symptomatic recurrent venous thromboembolism, which was defined as a composite of fatal or nonfatal pulmonary embolism or deep-vein thrombosis on the basis of criteria that have been described previously.[9] Death was classified as due to pulmonary embolism, bleeding, or other established diagnoses. Pulmonary embolism was considered the cause of death if there was objective documentation of the condition or if death could not be attributed to a documented cause and pulmonary embolism could not be confidently ruled out.

The principal safety outcome was clinically relevant bleeding, which was defined as a composite of major or clinically relevant nonmajor bleeding, as described previously.[9] Bleeding was defined as major if it was clinically overt and associated with a decrease in the hemoglobin level of 2.0 g per deciliter or more, if bleeding led to the transfusion of 2 or more units of red cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death. Clinically relevant nonmajor bleeding was defined

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

Characteristic	Rivaroxaban (N=2419)	Standard Therapy (N=2413)
Mean age — yr	57.9±7.3	57.5±7.2
Male sex — no. (%)	1309 (54.1)	1247 (51.7)
Weight — no. (%)		
≤50 kg	38 (1.6)	43 (1.8)
>50 to 100 kg	2034 (84.1)	2010 (83.3)
>100 kg	345 (14.3)	359 (14.9)
Missing data	2 (<0.1)	1 (<0.1)
Creatinine clearance — no. (%)		
<30 ml/min	4 (0.2)	2 (<0.1)
30 to <50 ml/min	207 (8.6)	191 (7.9)
50 to <80 ml/min	637 (26.3)	593 (24.6)
≥80 ml/min	1555 (64.3)	1617 (67.0)
Missing data	16 (0.7)	10 (0.4)
Diagnostic method — no. (%)		
Spiral computed tomography	2114 (87.4)	2076 (86.0)
Ventilation–perfusion lung scanning	284 (11.7)	326 (13.5)
Pulmonary angiography	20 (0.8)	10 (0.4)
Missing data	1 (<0.1)	1 (<0.1)
Anatomical extent of pulmonary embolism — no. (%)		
Limited: ≤25% of vasculature of a single lobe	309 (12.8)	299 (12.4)
Intermediate	1392 (57.5)	1424 (59.0)
Extensive: multiple lobes and >25% of entire pulmonary vasculature	597 (24.7)	576 (23.9)
Not assessable	121 (5.0)	114 (4.7)
Concurrent symptomatic deep-vein thrombosis — no. (%)	606 (25.1)	590 (24.5)
Hospitalized — no. (%)	2156 (89.1)	2160 (89.5)
Admitted to intensive care unit — no. (%)	311 (12.9)	289 (12.0)
Time from onset of symptoms to randomization — days		
Median	4.0	4.0
Interquartile range	2.0–8.0	2.0–9.0
Cause of pulmonary embolism — no. (%)†		
Unprovoked	1566 (64.7)	1551 (64.3)
Recent surgery or trauma	415 (17.2)	398 (16.5)
Immobilization	384 (15.9)	380 (15.7)
Estrogen therapy	207 (8.6)	223 (9.2)
Active cancer	114 (4.7)	109 (4.5)
Known thrombophilic condition — no. (%)	138 (5.7)	121 (5.0)
Previous venous thromboembolism — no. (%)	455 (18.8)	489 (20.3)

* Plus–minus values are means ±SD. There were no significant differences between the two study groups. Percentages may not total 100 because of rounding.
† Patients could have multiple causes of pulmonary embolism.

Table 2. Characteristics of Treatment.

Characteristic	Rivaroxaban (N=2419)	Standard Therapy (N=2413)	P Value
Prerandomization treatment with low-molecular-weight heparin, heparin, or fondaparinux — no. (%)	2237 (92.5)	2223 (92.1)	0.62
Duration of prerandomization treatment — no. (%)			0.56
1 day	1389 (57.4)	1400 (58.0)	
2 days	801 (33.1)	777 (32.2)	
>2 days	47 (1.9)	46 (1.9)	
At least one dose of a study drug received — no. (%)	2412 (99.7)	2405 (99.7)	0.79
Intended duration of treatment — no. (%)			0.95
3 mo	127 (5.3)	122 (5.1)	
6 mo	1387 (57.3)	1387 (57.5)	
12 mo	905 (37.4)	904 (37.5)	
Mean study duration — days	263	268	
Actual duration of treatment — days			
3-mo group			0.69
Median	93.0	92.0	
Interquartile range	91.0–97.0	90.0–96.0	
6-mo group			0.28
Median	182.0	181.0	
Interquartile range	179.0–184.0	178.0–183.0	
12-mo group			0.48
Median	355.0	354.0	
Interquartile range	278.0–358.0	274.0–357.0	
Mean study treatment duration — days	216	214	
Reasons for premature discontinuation of treatment — no. (%)			
Any reason	258 (10.7)	297 (12.3)	0.07
Adverse event	111 (4.6)	92 (3.8)	
Consent withdrawn	66 (2.7)	118 (4.9)	
Loss to follow-up	8 (0.3)	10 (0.4)	

as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life.[15]

Predefined secondary outcomes included major bleeding, death from any cause, vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism), and net clinical benefit (which was defined as a composite of the primary efficacy outcome and major bleeding, as assessed in the intention-to-treat population).

STATISTICAL ANALYSIS

The study was designed as an event-driven, noninferiority study. Assuming equal efficacy of the two study treatments, we determined that 88 events would provide a power of 90% to show that rivaroxaban was noninferior to standard therapy, using a margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio, with a two-sided alpha level of 0.05. The pro-

tocol specified that the steering committee would stop enrollment when it was estimated that 88 events would be reached. This decision was made without knowledge of the outcomes in the two study groups. When enrollment was discontinued, patients completed their assigned treatment except for those in the 12-month stratum who completed at least 6 months of treatment. Assuming a 3% incidence of the primary efficacy outcome, we expected to enroll at least 3000 patients.

Since the rivaroxaban regimen was derived from studies involving patients who had deep-vein thrombosis without symptomatic pulmonary embolism, we included a dose-confirmation phase in which the initial 400 patients underwent repeat lung imaging at 3 weeks. An independent dose-confirmation committee reviewed the incidence of the composite outcome of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat lung imaging. On the basis of the prespecified criterion that the one-sided 95% confidence interval for the between-group difference in the incidence of this outcome would not exceed 8.0%, the dose-confirmation

Table 3. Clinical Outcomes.

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Efficacy				
Intention-to-treat population — no. of patients	2419	2413		
Recurrent venous thromboembolism — no. (%)	50 (2.1)	44 (1.8)	1.12 (0.75–1.68)	0.003†
Type of first recurrent venous thromboembolism — no.				
Fatal pulmonary embolism	2	1		
Death in which pulmonary embolism could not be ruled out	8	5		
Nonfatal pulmonary embolism	22	19		
Recurrent deep-vein thrombosis plus pulmonary embolism	0	2		
Recurrent deep-vein thrombosis	18	17		
Net clinical benefit: venous thromboembolism plus major bleeding — no. (%)‡	83 (3.4)	96 (4.0)	0.85 (0.63–1.14)	0.28
Safety				
No. of patients	2412	2405		
First episode of major or clinically relevant nonmajor bleeding during treatment — no. (%)	249 (10.3)	274 (11.4)	0.90 (0.76–1.07)	0.23
Major bleeding episode — no. (%)				
Any	26 (1.1)	52 (2.2)	0.49 (0.31–0.79)	0.003
Fatal	2 (<0.1)	3 (0.1)		
Retroperitoneal	0	1 (<0.1)		
Intracranial	2 (<0.1)	2 (<0.1)		
Other nonfatal episode in a critical site§	7 (0.3)	26 (1.1)		
Intracranial	1 (<0.1)	10 (0.4)		
Retroperitoneal	1 (<0.1)	7 (0.3)		
Intraocular	2 (<0.1)	2 (<0.1)		
Pericardial	0	2 (<0.1)		
Intraarticular	0	3 (0.1)		
Adrenal gland	1 (<0.1)	0		
Hemothorax	1 (<0.1)	1 (<0.1)		
Intraabdominal with hemodynamic instability	1 (<0.1)	2 (<0.1)		
Associated with a fall in hemoglobin of ≥2 g/dl, transfusion of ≥2 units, or both	17 (0.7)	26 (1.1)		

Table 3. (Continued.)

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Clinically relevant nonmajor bleeding episode — no. (%)	228 (9.5)	235 (9.8)		
Death during intended treatment period — no. (%)	58 (2.4)	50 (2.1)	1.13 (0.77–1.65)	0.53
Cause of death — no.				
Pulmonary embolism or pulmonary embolism not ruled out¶	11	7		
Bleeding	5‖	4‖		
Cancer	20	23		
Myocardial infarction	2	1		
Ischemic stroke	2	1		
Other cardiac disorder or respiratory failure	4	4		
Infectious disease or septicemia	10	6		
Other	4	4		
Adverse event — no. (%)				
Any event emerging during treatment	1941 (80.5)	1903 (79.1)		0.24
Any serious event emerging during treatment	476 (19.7)	470 (19.5)		0.86
Any event resulting in permanent discontinuation of study drug	123 (5.1)	99 (4.1)		0.10
Any event leading to or prolonging hospitalization	475 (19.7)	430 (17.9)		0.82

* Hazard ratios are for rivaroxaban as compared with standard therapy.
† This P value is for noninferiority with a margin of 2.0. P=0.57 for superiority.
‡ Since the analysis of net clinical benefit is based on the intention-to-treat population and some patients had a major bleeding episode after cessation of a study drug, the numerator may exceed the sum of recurrences and major bleeding episodes reported in this table.
§ Some patients had more than one episode of major bleeding.
¶ One patient in each group had a second recurrent event that was fatal.
‖ Three patients in the rivaroxaban group and one patient in the standard-therapy group had a fatal bleeding episode when they were no longer taking a study medication.

committee recommended that the study be continued as planned.

The primary efficacy analysis was performed on an intention-to-treat basis with the use of a Cox proportional-hazards model stratified according to the intended duration of treatment, with adjustment for the presence or absence of cancer at baseline. Kaplan–Meier curves were generated to display the distribution of events over time. The population for the safety analysis was defined as all patients who received at least one dose of a study drug. Bleeding events were included in the analysis if they occurred during treatment or within 2 days after the last dose of a study drug. In addition, we performed analyses of the primary efficacy and principal safety outcomes in prespecified subgroups.

The mean time during which the INR was in the therapeutic range was calculated after the discontinuation of enoxaparin, with correction for interruptions in the administration of vitamin K antagonists.

RESULTS

PATIENTS

From March 2007 through March 2011, we enrolled 4832 patients — 2419 who were assigned to receive rivaroxaban and 2413 who were assigned to receive enoxaparin and a vitamin K antagonist (standard therapy) — at 263 sites in 38 countries (Fig. 1). The characteristics of the patients were similar at baseline (Table 1).

TREATMENT AND FOLLOW-UP

Data on treatment in the two study groups and 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 more in 83% of patients. The percentage of time during which the INR was in the therapeutic range (2.0 to 3.0) was 62.7%; the corresponding percentages for an INR above 3.0 and

below 2.0 were 15.5% and 21.8%. The percentage of time within the therapeutic range ranged from 57.8% (during the first month) to 72.7% (during month 11). In the rivaroxaban group, adherence to therapy was above 80% in 94.2% of patients.

As a result of termination of the event-driven study, the treatment duration was less than intended in 125 patients (5.2%) in the rivaroxaban group and 132 patients (5.5%) in the standard-therapy group. A total of 8 patients (0.3%) in the rivaroxaban group and 10 patients (0.4%) in the standard-therapy group were lost to follow-up.

CLINICAL OUTCOMES

The clinical outcomes are shown in Table 3. Recurrent nonfatal venous thromboembolism was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard-therapy group. The primary efficacy outcome occurred in 50 patients (2.1%) in the rivaroxaban group as compared with 44 patients (1.8%) in the standard-therapy group, for a hazard ratio of 1.12 (95% confidence interval [CI], 0.75 to 1.68; P=0.003 for a one-sided noninferiority margin of 2.0 and P=0.57 for superiority). By day 21, at the end of twice-daily rivaroxaban administration, the primary efficacy outcome had occurred in 18 patients (0.7%) in the rivaroxaban group and in 21 patients (0.9%) in the standard-therapy group (Fig. 2A). The results of the on-treatment and per-protocol analyses were similar to those of the intention-to-treat analysis, with hazard ratios of 1.12 (95% CI, 0.73 to 1.72) and 1.07 (95% CI, 0.70 to 1.63), respectively (data not shown).

The rates of recurrent venous thromboembolism among patients with anatomically limited, intermediate, or extensive pulmonary embolism at baseline were 1.6% (5 of 309 patients), 2.5% (35 of 1392), and 1.7% (10 of 597), respectively, in the rivaroxaban group and 1.3% (4 of 299), 2.2% (31 of 1424), and 1.4% (8 of 576), respectively, in the standard-therapy group.

The principal safety outcome, a first major or clinically relevant nonmajor bleeding episode, occurred in 249 patients (10.3%) in the rivaroxaban group as compared with 274 patients (11.4%) in the standard-therapy group (hazard ratio, 0.90; 95% CI, 0.76 to 1.07; P=0.23) (Fig. 2B). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and in 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79, P=0.003) (Fig. 2C).

Figure 2 (facing page). Cumulative Rates of the Primary Efficacy and Safety Outcomes and Rates of Major Bleeding.

Shown are Kaplan–Meier cumulative event rates for the primary efficacy outcome of symptomatic recurrent venous thromboembolism (P=0.003 for noninferiority) (Panel A), for the principal safety composite outcome of major or clinically relevant nonmajor bleeding (P=0.23) (Panel B), and for major bleeding (P=0.003) (Panel C).

The outcome of a net clinical benefit occurred in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the standard-therapy group (hazard ratio, 0.85; 95% CI, 0.63 to 1.14; P=0.28). The relative primary efficacy and principal safety outcomes across the prespecified subgroups were consistent with the observed overall effects (see the Supplementary Appendix, available at NEJM.org).

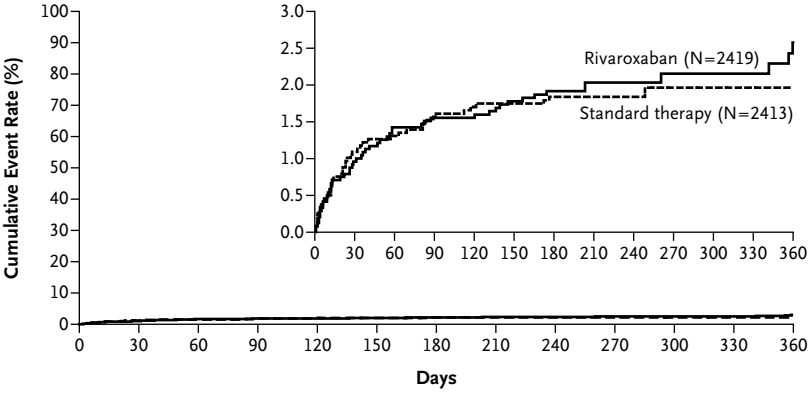
Among the patients who were included in the safety analysis, acute coronary events during treatment occurred in 15 of 2412 patients (0.6%) in the rivaroxaban group and in 21 of 2405 patients (0.9%) in the standard-therapy group. The corresponding rates in the 30-day post-study treatment period were 0.1% in both groups. Further details regarding the vascular outcomes are provided in the Supplementary Appendix.

The combination of an alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range was observed in five patients (0.2%) in the rivaroxaban group and four (0.2%) in the standard-therapy group.

DISCUSSION

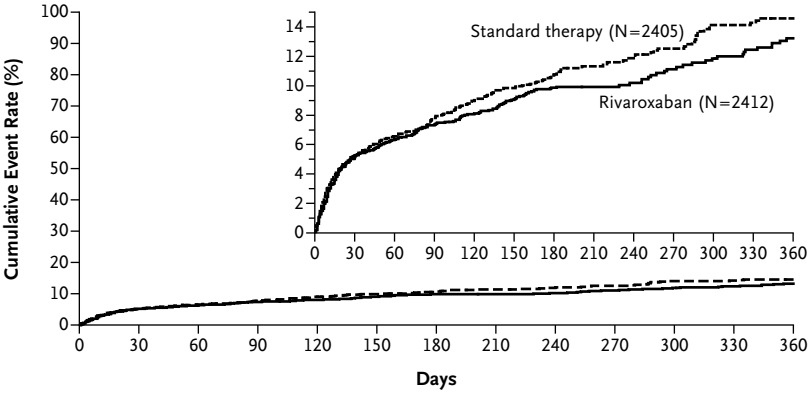
In this study involving patients with symptomatic pulmonary embolism, oral rivaroxaban alone provided protection from recurrent venous thromboembolism that was similar to the protection provided by standard therapy, with similar bleeding rates. During a mean study duration of approximately 9 months, there was a recurrence in 2.1% of patients in the rivaroxaban group and 1.8% of those in the standard-therapy group. The primary safety outcome of major or clinically relevant nonmajor bleeding was observed in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group, and major bleeding was observed in 1.1% and 2.2% of patients,

A Primary Efficacy



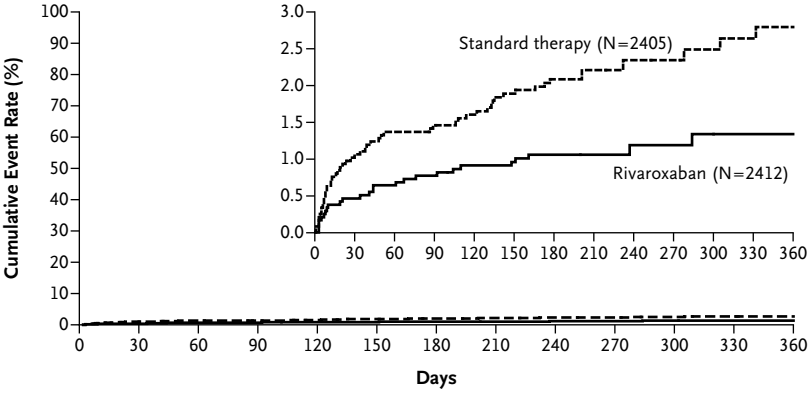
No. at Risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Standard therapy	2413	2316	2295	2273	2155	2146	2050	835	787	772	746	722	675

B Clinically Significant Bleeding



No. at Risk													
Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Standard therapy	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

C Major Bleeding



No. at Risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Standard therapy	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

respectively. Our observations are consistent with those of other trials in which rates of recurrence of thromboembolism in the standard-therapy group were 1.6 to 2.7% and the corresponding rates of major bleeding were 1.4 to 2.4%.[8,9]

In previous studies involving patients with pulmonary embolism before the advent of new compounds (idrabiotaparinux or dabigatran etexilate), low-molecular-weight heparin was used as initial therapy.[8,17] In our study, we tested the concept of a single-drug approach with an oral compound in a large population of patients with pulmonary embolism.

Several aspects of this study deserve comment. We believe that our population is representative of the spectrum of patients who present with symptomatic pulmonary embolism, with the exception of those for whom fibrinolytic therapy is planned. A total of 1173 patients (nearly 25%) in our study met our definition of extensive disease, and 608 (13%) had limited pulmonary embolism. Furthermore, nearly 25% had concomitant symptomatic deep-vein thrombosis. The baseline characteristics of the patients, including the presence of risk factors, were similar to those in previous studies of pulmonary embolism.[7-9] In keeping with current practice, the duration of treatment was 3, 6, or 12 months, with most patients receiving 6 months or more of therapy.

We analyzed factors that may have influenced outcomes. Specifically, the quality of standard therapy was well within clinical acceptability, with the INR in the therapeutic range 62.7% of the time and exceeding 3.0 only 15.5% of the time. These results compare favorably with the findings in other contemporary studies of venous thromboembolism.[8,15,17] Adherence to the rivaroxaban regimen was high in 94% of patients. The number of patients who were lost to follow-up was negligible.

The suggestion that rivaroxaban can be administered at the same dose in all patients without laboratory monitoring has raised concern. Therefore, we performed multiple subgroup analyses for both efficacy and safety. Rates of recurrent venous thromboembolism and bleeding were similar in the two study groups regardless of age, sex, presence or absence of obesity, level of renal function, or extent of pulmonary embolism.

We decided to start therapy with an intensive rivaroxaban regimen (15 mg twice daily) for the first 3 weeks for two reasons. In previous studies, failure to provide adequate initial therapy led to unacceptable recurrence rates.[4,9,18,19] In addition, in phase 2 studies, the use of twice-daily rivaroxaban led to an earlier steady state, higher trough levels, and better thrombus regression at 3 weeks than did once-daily administration.[20,21] In our study, the Kaplan–Meier curves for recurrence with this regimen and with standard therapy were identical. One concern about the intensified initial dose of rivaroxaban was that it could potentially increase the risk of hemorrhage. However, during the initial period, the bleeding rates were similar in the two study groups, with fewer major bleeding events in the rivaroxaban group. Furthermore, during the entire course of treatment, there were fewer episodes of intracranial bleeding or bleeding in critical areas in the rivaroxaban group than in the standard-therapy group. The explanation for this finding requires further study.

Before randomization, almost all patients received low-molecular-weight heparin, which is unavoidable in clinical trials of venous thromboembolism, since such treatment is consistent with current practice pending confirmation of the diagnosis. In nearly 60% of patients in our study, this therapy was limited to 1 day, and less than 2% of patients received more than 2 days of treatment before enrollment. It seems unlikely that this brief exposure would have significant effects on the study outcomes.

Since the study had an open design, there is a potential for a diagnostic-suspicion bias. Indeed, the absolute number of patients with suspected recurrence was higher in the rivaroxaban group, and the proportions of patients with confirmed events were similar in the two groups (10.2% in the rivaroxaban group and 9.7% in the standard-therapy group). This finding suggests that the open design may have caused a slight bias against rivaroxaban. Careful follow-up revealed similarly low rates of both acute coronary events and changes in liver-function tests in the two study groups.

Our findings in this study involving patients with pulmonary embolism, along with those of our previous evaluation involving patients with deep-vein thrombosis,[15] support the use of rivaroxaban as a single oral agent for patients with venous thromboembolism.

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APPENDIX

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