ORIGINAL ARTICLE

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty

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ABSTRACT

BACKGROUND

We investigated the efficacy of rivaroxaban, an orally active direct factor Xa inhibitor, in preventing venous thrombosis after total knee arthroplasty.

METHODS

In this randomized, double-blind trial, 2531 patients who were to undergo total knee arthroplasty received either oral rivaroxaban, 10 mg once daily, beginning 6 to 8 hours after surgery, or subcutaneous enoxaparin, 40 mg once daily, beginning 12 hours before surgery. The primary efficacy outcome was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days after surgery. Secondary efficacy outcomes included major venous thromboembolism (i.e., proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism) and symptomatic venous thromboembolism. The primary safety outcome was major bleeding.

RESULTS

The primary efficacy outcome occurred in 79 of 824 patients (9.6%) who received rivaroxaban and in 166 of 878 (18.9%) who received enoxaparin (absolute risk reduction, 9.2%; 95% confidence interval [CI], 5.9 to 12.4; $P<0.001$). Major venous thromboembolism occurred in 9 of 908 patients (1.0%) given rivaroxaban and 24 of 925 (2.6%) given enoxaparin (absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8; $P=0.01$). Symptomatic events occurred less frequently with rivaroxaban than with enoxaparin ($P=0.005$). Major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% of patients in the enoxaparin group. The incidence of drug-related adverse events, mainly gastrointestinal, was 12.0% in the rivaroxaban group and 13.0% in the enoxaparin group.

CONCLUSIONS

Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding. (ClinicalTrials.gov number, NCT00361894.)

Venous thromboembolism is a major, potentially fatal complication after major orthopedic surgery such as total knee arthroplasty.[1] Anticoagulants that are currently used for thromboprophylaxis require parenteral administration or have unpredictable pharmacodynamic properties that require monitoring.[2] Several anticoagulants currently in development target individual coagulation factors, including thrombin and activated factor X (factor Xa). The efficacy of the parenterally administered indirect factor Xa inhibitor fondaparinux for thromboprophylaxis encouraged the development of direct factor Xa inhibitors.[3]

Rivaroxaban (Xarelto, Bayer HealthCare) is an orally active direct factor Xa inhibitor.[4] Phase 2 studies showed that rivaroxaban was potentially safe and effective for thromboprophylaxis after major orthopedic surgery across a wide range of doses.[5-8] Total daily doses of 5 to 20 mg of rivaroxaban had efficacy and safety similar to those of enoxaparin after total hip arthroplasty and total knee arthroplasty.[6,7] A subsequent study indicated that rivaroxaban at a dose of 10 mg once daily had sufficient efficacy and safety to merit further investigation.[8]

Here, we describe a multicenter, randomized, double-blind trial that compared the efficacy and safety of oral rivaroxaban, 10 mg once daily, administered postoperatively, with those of enoxaparin, 40 mg given subcutaneously once daily, administered preoperatively, for the prevention of venous thromboembolism after elective total knee arthroplasty.

METHODS

PATIENTS

Patients were eligible for the study if they were 18 years of age or older and were scheduled for total knee arthroplasty. We excluded patients with active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin and patients with any contraindication to the use of enoxaparin or with any contraindication necessitating adjustment of its dose. Other exclusion criteria included conditions preventing bilateral venography, clinically significant liver disease, concomitant use of protease inhibitors of the human immunodeficiency virus or fibrinolytic agents, planned intermittent pneumatic compression, requirement of ongoing anticoagulant therapy, and pregnancy or breast-feeding.

STUDY DESIGN AND MEDICATIONS

On a double-blind and double-dummy basis, before surgery, patients were randomly assigned through a central telephone system to receive once-daily oral rivaroxaban (Bayer HealthCare), in a 10-mg tablet, or a once-daily injection of enoxaparin sodium (Clexane or Lovenox, Sanofi-Aventis), in a 40-mg dose. Enoxaparin was initiated 12 hours before surgery and was given again 6 to 8 hours after wound closure. Rivaroxaban was initiated 6 to 8 hours after wound closure. Thereafter, the study medication was administered every 24 hours.

The day of surgery was defined as day 1, and study medications were continued until at least day 10 and up to day 14. Patients underwent mandatory, bilateral venography between day 11 and day 15. No further study medication was given after venography; further thromboprophylaxis was given at the investigator's discretion, according to the local practice. Patients were followed for 30 to 35 days after the last dose of study medication.

The trial was performed in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee or institutional review board of each center, and written informed consent was obtained from each patient before randomization.

The study was designed and supervised by the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD3) Steering Committee (see the Appendix). Data were collected and analyzed by the study sponsors. The Steering Committee wrote the first draft of the manuscript and made the decision to publish. All authors contributed to writing the manuscript, had full access to the data and analyses, and vouch for the report's accuracy and completeness.

OUTCOME MEASURES

All outcomes were assessed by central, independent adjudication committees who were unaware of the treatment assignments. The primary outcome was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days after surgery. The main secondary efficacy outcome was major venous thromboembolism (i.e., proximal deep-vein

thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism). Other efficacy outcomes included the incidence of deep-vein thrombosis (any, proximal, or distal), symptomatic venous thromboembolism occurring during the treatment period or follow-up period, and death during the follow-up period.

Deep-vein thrombosis was assessed between day 11 and day 15, or earlier if symptoms were present, by means of ascending, bilateral venography.[9] In cases of suspected deep-vein thrombosis, ultrasonography or venography was used to confirm the diagnosis. In cases of suspected pulmonary embolism, ventilation–perfusion scintigraphy of the lung and chest radiography or spiral computed tomography were performed, or pulmonary angiography was performed. Autopsies were planned if a participant died.

The main safety outcome was the incidence of major bleeding occurring between intake of the first dose of study medication and 2 days after the last dose. Major bleeding was defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the hemoglobin level of 2 g or more per deciliter or requiring infusion of 2 or more units of blood. Other safety outcomes included any bleeding or major bleeding occurring between intake of the first dose of study medication and 2 days after the last dose, nonmajor bleeding including hemorrhagic wound complications (excessive wound hematoma or bleeding at the surgical site), other adverse events, and death. Laboratory variables and cardiovascular adverse events were monitored during the treatment and follow-up periods.

STATISTICAL ANALYSIS

We aimed to determine whether the efficacy of rivaroxaban was noninferior to that of enoxaparin in the per-protocol population and, if so, to determine whether rivaroxaban had superior efficacy to enoxaparin in the modified intention-to-treat population. The modified intention-to-treat population included all patients who had undergone surgery, who took a study medication, and who had an adequate assessment for thromboembolism. These patients were included in the per-protocol analysis if their records showed no major protocol violations. The safety analysis included all patients who received at least one dose of a study medication.

For the primary efficacy analysis, we estimated the difference between the incidences in the rivaroxaban group and the enoxaparin group, after stratification on the basis of country of the center, using Mantel–Haenszel weighting; the corresponding asymptotic two-sided 95% confidence interval was also reported. Tests for noninferiority and superiority were both based on 95% confidence intervals. For the primary efficacy outcome, the threshold for the noninferiority test was an absolute difference between the two groups of 4%. The superiority test for major venous thromboembolism was preceded by a noninferiority test (absolute margin, 1.5%). Unweighted exact methods were used to assess secondary outcomes that occurred infrequently (e.g., pulmonary embolism and death).

For the test of superiority, on the basis of an assumed event rate of 27% in the enoxaparin group, we calculated that 860 patients per treatment group would be sufficient to detect a relative risk reduction of 25% in the rivaroxaban group as compared with the enoxaparin group, with a statistical power of 90% and a two-sided type I error rate of 5%. With the assumption of an inadequate assessment of venous thromboembolism in 25% of participants, the total number of patients was increased to 2300.

In the two-step statistical analysis we performed, a noninferiority test (based on a noninferiority limit of 4 percentage points) preceding the superiority test had a statistical power of 91% if we assumed an absolute risk reduction of 3% (corresponding to a relative risk reduction of 11%) in the rivaroxaban group as compared with the enoxaparin group. If the absolute risk reduction was assumed to be only 2% (corresponding to a relative risk reduction of 7%), a statistical power of 80% would be maintained.

The difference in the incidence of major bleeding between the rivaroxaban group and the enoxaparin group was analyzed with the same methods for efficacy; other safety outcomes were analyzed by means of appropriate descriptive methods. Sex and race were analyzed with the use of a Cochran–Mantel–Haenszel test adjusted for country. Age, weight, and body-mass index were analyzed by means of two-way analysis of variance, with treatment group and country as fixed effects. All other variables were analyzed descriptively, and statistical tests were performed with the use of a two-sided type I error rate of 5%.

RESULTS

STUDY POPULATIONS

Between February 2006 and November 2006, 2556 patients were enrolled in 147 centers in 19 countries (Fig. 1). Reasons for exclusion were similar between the rivaroxaban and enoxaparin groups (Table 1). Baseline characteristics were well balanced between the two groups except for a slight excess of women in the rivaroxaban group (P=0.03) (Table 2). The mean duration of therapy was 11.9 days with rivaroxaban and 12.5 days with enoxaparin.

EFFICACY OUTCOMES

The primary efficacy outcome occurred in 79 of 824 patients (9.6%) in the rivaroxaban group and in 166 of 878 (18.9%) in the enoxaparin group (weighted absolute risk reduction, 9.2%; 95% confidence interval [CI], 5.9 to 12.4; P<0.001; relative risk reduction, 49%; 95% CI, 35 to 61; P<0.001) (Table 3). Rivaroxaban was noninferior to enoxaparin (P<0.001 for the noninferiority analysis; data not shown).

Major venous thromboembolism occurred in 9 of 908 patients (1.0%) in the rivaroxaban group and 24 of 925 (2.6%) in the enoxaparin group (weighted absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8; P=0.01; relative risk reduction, 62%; 95% CI, 18 to 82; P=0.02) (Table 3).

Among the 2418 patients who were validated for the safety analysis and who underwent surgery, the incidence of symptomatic venous thromboembolic events was lower in the rivaroxaban group (8 of 1201 patients [0.7%]) than in the enoxaparin group (24 of 1217 patients [2.0%]; weighted absolute risk reduction, 1.3%; 95% CI, 0.4 to 2.2; P=0.005; relative risk reduction, 66%; 95% CI, 25 to 85; P=0.008) (Table 3). The incidence of symptomatic venous thromboembolism during the follow-up period was similar in the two groups (Table 3). During the treatment period, there were no deaths or known pulmonary emboli in the rivaroxaban group and two unexplained deaths and four known pulmonary emboli in the enoxaparin group; during the follow-up period, there were four unexplained deaths in the enoxaparin group.

SAFETY

Major bleeding occurred in 7 of 1220 patients (0.6%) who received rivaroxaban and 6 of 1239 (0.5%) who received enoxaparin (weighted absolute risk increase, 0.1%; P=0.77) (Table 4). No episodes of fatal bleeding occurred. There were three cases of hemorrhagic spinal puncture without neurologic signs or symptoms of compression: one occurred in the rivaroxaban group before the first dose was administered, and two occurred in the enoxaparin group. The combined incidence of major and clinically relevant nonmajor bleeding events was similar in the two groups (40 of 1220 patients [3.3%] in the rivaroxaban group and 34 of 1239 patients [2.7%] in the enoxaparin group, P=0.44). There was no significant difference between the two groups in postoperative drainage or transfusion requirement (Table 4).

The adverse-event profiles of rivaroxaban and enoxaparin were similar (Table 4 and the Supplementary Appendix, available with the full text of this article at www.nejm.org); the most commonly reported events in both groups included nausea, vomiting, and constipation. The incidences of serious events and serious drug-related events were also similar in the two groups during treatment. There were six deaths (0.5%) during the entire study, all in the enoxaparin group. Alanine aminotransferase levels were elevated to three times the upper limit of the normal range in 20 of 1150 patients (1.7%) who were receiving rivaroxaban and in 20 of 1156 patients (1.7%) who were receiving enoxaparin; two of these patients in the rivaroxaban group also had serum bilirubin levels that were more than twice the upper limit of the normal range. In all these patients, the increased levels of alanine aminotransferase and bilirubin returned to normal with continued treatment. The incidence of adverse cardiovascular events during therapy was low and was similar between the two groups (Table 4). During the follow-up period, there were no cardiovascular events in the rivaroxaban group and seven events in six patients receiving enoxaparin.

DISCUSSION

In this trial of thromboprophylaxis after total knee arthroplasty, we found that rivaroxaban, an orally active direct inhibitor of factor Xa, was more effective than enoxaparin in preventing venous thrombosis, with similar rates of bleeding. Rivaroxaban reduced the absolute risk of the composite of deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause by 9.2%, and the risk of major venous thromboembolism by 1.6%, as com-

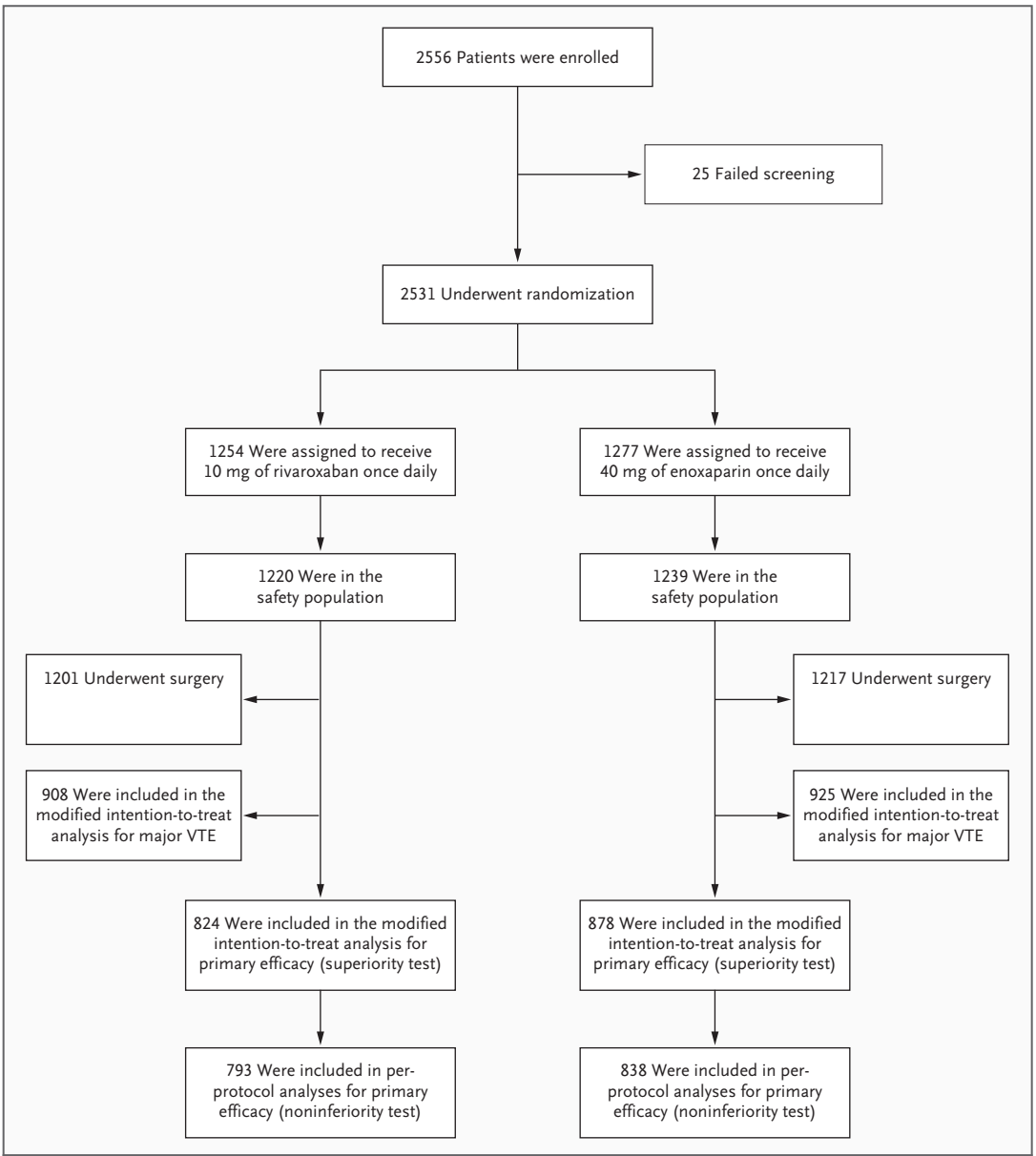

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

Patients were included in the modified intention-to-treat population for major venous thromboembolism (VTE) if only the proximal veins were assessed.

pared with enoxaparin. The absolute risk reduction in the incidence of clinically important, symptomatic venous thromboembolic events was also greater with rivaroxaban than enoxaparin (absolute risk reduction, 1.3%). There were no pulmonary emboli or deaths in patients receiving rivaroxaban; in the enoxaparin group, four patients had a pulmonary embolus and an additional two died.

Rivaroxaban and enoxaparin had similar safety profiles. There were no clinically significant differences in the incidence of bleeding or other safety outcomes between the two groups. Major bleeding occurred in 0.6% of patients in the rivaroxaban group and in 0.5% of patients in the enoxaparin group. These rates are in line with the rates found in similar trials.[10,11] Bleeding was defined in this trial as bleeding occurring after the intake of the first blinded dose of study medica-

Table 1. Inclusion and Exclusion of the Study Participants Who Underwent Randomization.

Characteristic	Rivaroxaban (N=1254)	Enoxaparin (N=1277)
	no. (%)	
Excluded because they did not take study medication	34 (2.7)	38 (3.0)
Included in safety analysis	1220 (97.3)	1239 (97.0)
Excluded because they did not undergo surgery	19 (1.5)	22 (1.7)
Eligible for assessment of symptomatic venous thromboembolism	1201 (95.8)	1217 (95.3)
Eligible for assessment of major venous thromboembolism (modified intention-to-treat population)*	908 (72.4)	925 (72.4)
Eligible for superiority efficacy analysis (modified intention-to-treat population)	824 (65.7)	878 (68.8)
Excluded because of inadequate assessment of thromboembolism	376 (30.0)	339 (26.5)
Venography not performed	156 (41.5)	166 (49.0)
Unilateral venography	82 (21.8)	69 (20.4)
Venogram indeterminate or could not be evaluated	131 (34.8)	96 (28.3)
Venography performed outside time window†	7 (1.9)	8 (2.4)
Eligible for noninferiority efficacy analysis (per-protocol population)	793 (63.2)	838 (65.6)
Incorrect time interval between end of surgery and first postoperative dose of study drug	10 (0.8)	17 (1.3)
Incorrect time interval between last dose of study drug and venography	9 (0.7)	15 (1.2)
Insufficient compliance	5 (0.4)	7 (0.5)
Compliance >120%	5 (0.4)	0
Intake of prohibited anticoagulant	2 (0.2)	1 (0.1)

* Patients were eligible for the assessment of major venous thromboembolism if proximal veins could be evaluated on the venogram, regardless of whether or not the distal veins could be evaluated.
† The time window for adequate venography was day 9 to day 17, unless there was a positive finding earlier.

tion. In the rivaroxaban group, bleeding that occurred during or shortly after surgery was included (1 major bleeding event and 10 nonmajor bleeding events), even though rivaroxaban had not been administered. This design resulted in a conservative estimate of the incidence of bleeding with rivaroxaban. Elevations of alanine aminotransferase and bilirubin levels, found in less than 2% of patients in both groups, were transient and returned to normal during treatment, as has been found in other trials.[6-8,12]

There is a risk of reactivation of coagulation on cessation of anticoagulant treatment, which may manifest as an increase in adverse cardiovascular events.[13] Such events (cardiovascular death, myocardial infarction, ischemic stroke, or unexplained death) were specifically monitored and centrally adjudicated as a safety outcome. None occurred after cessation of treatment with rivaroxaban (with seven such events occurring in the enoxaparin group).

The strengths of this trial include the number of patients enrolled — more than in similar trials conducted with fondaparinux or ximelagatran.[10,11,14] The large number of nonwhite patients enrolled and the low number of excluded concomitant medications allow these findings to be applied widely. The incidence of deep-vein thrombosis in the enoxaparin group (18.2%) was consistent with the incidence in contemporary clinical trials of the direct factor Xa inhibitors razaxaban (15.9% of patients given enoxaparin)[15] and apixaban (15.6% of patients given enoxaparin).[16] The incidence of major venous thromboembolism (the composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism) among patients receiving enoxaparin was 2.2%[17] and 3.1%,[18] in studies investigating dabigatran and ximelagatran, respectively, as compared with 2.6% in this trial — suggesting that enoxaparin performed well in this trial.

Table 2. Baseline Characteristics of the 2459 Patients in the Safety Population.

Characteristic	Rivaroxaban (N=1220)	Enoxaparin (N=1239)
Female sex — no. (%)*	857 (70.2)	821 (66.3)
Age — yr		
Mean	67.6	67.6
Range	28–91	30–90
Weight — kg		
Mean	80.1	81.2
Range	45–150	41–157
Body-mass index†		
Mean	29.5	29.8
Range	16.3–51.1	16.0–54.3
Race or ethnic group — no. (%)‡		
White	1000 (82.0)	997 (80.5)
Asian	76 (6.2)	82 (6.6)
Hispanic	46 (3.8)	54 (4.4)
Black	15 (1.2)	13 (1.0)
Other or missing data	83 (6.8)	93 (7.5)
History of venous thromboembolism — no. (%)	48 (3.9)	42 (3.4)
Previous orthopedic surgery — no. (%)	384 (31.5)	325 (26.2)
Type of surgery — no. (%)		
Primary	1176 (96.4)	1186 (95.7)
Revision of implants	24 (2.0)	30 (2.4)
None or missing data	20 (1.6)	23 (1.9)
Type of anesthesia — no. (%)		
General only	227 (18.6)	242 (19.5)
General and regional	188 (15.4)	201 (16.2)
Regional only	786 (64.4)	774 (62.5)
None	19 (1.6)	22 (1.8)
Duration of surgery — min		
Mean	96.4	97.1
Range	26–500	28–315

* The number of female patients was significantly different between the two groups (P=0.03).
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported.

In agreement with other phase 3 studies of thromboprophylaxis in patients undergoing major orthopedic surgery, the population used for the efficacy analysis did not include patients with an inadequate venographic assessment for the presence or absence of deep-vein thrombosis.[19,20] In our study, 67% of patients who underwent randomization were included in the modified intention-to-treat population. However, because the number of valid venograms was lower than expected, the steering committee (which was unaware of the treatment assignments) increased recruitment from the planned 2300 patients to more than 2500 to maintain the statistical power of the trial. To support the findings for the primary efficacy outcome, several sensitivity analyses were performed to ensure that missing data did not bias the outcome. All these analyses support the main finding of the study: a significant reduction in the incidence of the primary outcome with rivaroxaban, as compared with enoxaparin, with the exception of the most conservative assumption (i.e., that all

Table 3. Incidence of Events for Efficacy Analysis.*

Event	Rivaroxaban (N=1220)		Enoxaparin (N=1239)		Absolute Risk Difference	P Value
	No. with events/ total no.	% (95% CI)	No. with events/ total no.	% (95% CI)	% (95% CI)	
Up to day 17						
Primary efficacy outcome†	79/824	9.6 (7.7 to 11.8)	166/878	18.9 (16.4 to 21.7)	–9.2 (–12.4 to –5.9)	<0.001
Death	0/824	0.0 (0.0 to 0.5)	2/878	0.2 (0.0 to 0.8)	–0.2 (–0.8 to 0.2)	0.23
Pulmonary embolism	0/824	0.0 (0.0 to 0.3)	4/878	0.5 (0.1 to 1.2)	–0.5 (–1.2 to 0.0)	0.06
Deep-vein thrombosis	79/824	9.6 (7.7 to 11.8)	160/878	18.2 (15.7 to 20.9)	–8.4 (–11.7 to –5.2)	<0.001
Proximal	9/824	1.1 (0.5 to 2.1)	20/878	2.3 (1.4 to 3.5)	–1.1 (–2.3 to 0.1)	0.07
Distal	70/824	8.5 (6.7 to 10.6)	140/878	15.9 (13.6 to 18.5)	–7.3 (–10.4 to –4.3)	<0.001
Major venous thromboembolism (modified intention-to-treat population)‡	9/908	1.0 (0.5 to 1.9)	24/925	2.6 (1.7 to 3.8)	–1.6 (–2.8 to –0.4)	0.01
Death§	0/1201	0.0 (0.0 to 0.3)	2/1217	0.2 (0.02 to 0.6)	–0.2 (–0.6 to 0.2)	0.21
Pulmonary embolism§	0/1201	0.0 (0.0 to 0.3)	4/1217	0.3 (0.1 to 0.8)	–0.3 (–0.8 to 0.0)	0.05
Symptomatic venous thromboembolism§¶	8/1201	0.7 (0.3 to 1.3)	24/1217	2.0 (1.3 to 2.9)	–1.3 (–2.2 to –0.4)	0.005
During follow-up‖						
Symptomatic venous thromboembolism§¶	5/1201	0.4 (0.1 to 1.0)	3/1217	0.2 (0.1 to 0.7)	0.2 (–0.3 to 0.6)	0.44
Death§	0/1201	0.0 (0.0 to 0.3)	4/1217	0.3 (0.1 to 0.8)	–0.3 (–0.8 to 0.0)	0.05

* Absolute risk differences and P values were calculated with the use of the Mantel–Haenszel weighted estimator, except death and pulmonary embolism, for which unweighted risk reductions with the exact confidence interval are given.
† The primary efficacy outcome was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause in the modified intention-to-treat population.
‡ Major venous thromboembolism was the composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, and death related to venous thromboembolism. Patients were eligible for this analysis if only proximal veins were assessed by means of venography.
§ Patients were eligible for this analysis if they were included in the safety analysis and also underwent surgery.
¶ Symptomatic venous thromboembolism was defined as any symptomatic deep-vein thrombosis (proximal or distal) or symptomatic nonfatal or fatal pulmonary embolism.
‖ The follow-up period was day 30 to day 35 after the last dose of study medication.

Table 4. Safety Outcomes.

Outcome	Rivaroxaban (N=1220)	Enoxaparin (N=1239)	P Value for Difference
Any bleeding between start of treatment and 2 days after last dose — no. (% [95% CI])	60 (4.9 [3.8–6.3])	60 (4.8 [3.7–6.2])	0.93
Major bleeding between start of treatment and 2 days after last dose — no. (% [95% CI])*	7 (0.6 [0.2–1.2])	6 (0.5 [0.2–1.1])	0.77
Fatal bleeding — no. (%)	0	0	
Bleeding into a critical organ — no. (%)	0	1 (0.1)	
Bleeding leading to reoperation — no. (%)	5 (0.4)	4 (0.3)	
Clinically overt bleeding, outside of surgical site, leading to a decreased hemoglobin level — no. (%)	1 (0.1)	0	
Clinically overt bleeding, outside the surgical site, leading to transfusion of ≥2 units of blood — no. (%)	1 (0.1)	0	
Hemorrhagic spinal puncture or other — no. (%)	1 (0.1)†	1 (0.1)	
Nonmajor bleeding between start of treatment and 2 days after last dose — no. (% [95% CI])	53 (4.3 [3.3–5.6])	54 (4.4 [3.3–5.7])	
Clinically relevant nonmajor bleeding — no. (% [95% CI])	33 (2.7 [1.9–3.8])	28 (2.3 [1.5–3.3])	
Hemorrhagic wound complications — no. (%)‡	25 (2.0)	24 (1.9)	
Other nonmajor bleeding — no. (% [95% CI])	22 (1.8 [1.1–2.7])	31 (2.5 [1.7–3.5])	
Postoperative infection of wound — no. (%)§	7 (0.6)	11 (0.9)	
Bleeding between start of rivaroxaban or oral placebo and 2 days after last dose — no./total no. (%)¶	49/1191 (4.1)	55/1210 (4.5)	
Receipt of blood transfusions — no. (%)	619 (50.7)	575 (46.4)	
Volume of blood transfusion — ml			
Median	560	599	
Range	25–3300	100–3597	
Patients with postoperative drain — no. (%)	1043 (85.5)	1049 (84.7)	
Volume in drain — ml			
Median	600	600	
Range	15–3429	10–3072	
Any adverse event between start of treatment and 2 days after last dose — no. (%)	776 (63.6)	844 (68.1)	
Drug-related adverse event — no. (%)	146 (12.0)	161 (13.0)	
Cardiovascular adverse event ≤1 day after last dose of study medication — no. (%)	4 (0.3)	3 (0.2)	
Cardiovascular death	0	1 (0.1)	
Ischemic stroke	3 (0.2)	0	
Myocardial infarction	1 (0.1)	2 (0.2)	
≥1 Cardiovascular adverse event >1 day after the last dose of study medication — no. (%)	0	6 (0.5)	

* Patients may have had more than one type of event.
† Event occurred before receipt of the first dose of rivaroxaban.
‡ Hemorrhagic wound complications were defined as a composite of excessive wound hematoma and reported bleeding at the surgical site.
§ Postoperative infection of wound was classified according to the Medical Dictionary for Regulatory Activities (MedDRA, a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations).
¶ These bleeding events were evaluated among the subjects who were eligible for the safety analysis and who took at least one tablet (rivaroxaban or placebo).

patients with an inadequate assessment of thromboembolism were assumed to have had an event).

However, all patients were followed clinically and were included in the evaluation of symptomatic venous thromboembolism (see the Supplementary Appendix). All adjudicated events — positive venograms, symptomatic events, and deaths — and all venograms that could be evaluated and that were adjudicated to show no deep-vein thrombosis were considered, irrespective of whether they occurred outside the predefined time windows. The weighted absolute risk reduction for the primary outcome with rivaroxaban, as compared with enoxaparin, was 8.9% (95% CI, 5.6 to 12.2). Moreover, when all assessments by investigators that could be evaluated (when the assessment by the central adjudication committee could not be) were also included in the analysis, the weighted absolute risk reduction was 8.1%, in favor of rivaroxaban (95% CI, 4.9 to 11.2).

The optimal absolute risk margin for noninferiority studies is still debated. The margin has to be viewed in relation to the expected efficacy rate in the comparison group and to the clinical implication. Given the efficacy data from the phase 2 studies of rivaroxaban and the contemporary data on the comparison group, we found that a margin of 4 percentage points was acceptable. In this study, rivaroxaban was superior to enoxaparin, making the question of noninferiority moot.

We conducted our trial using the enoxaparin dose and regimen (40 mg once daily) approved for use in Europe, not the regimen (30 mg twice daily) approved for use after total knee arthroplasty in the United States. However, a trial is being conducted to compare rivaroxaban with the 30-mg, twice-daily dose of enoxaparin given before surgery in patients undergoing total knee arthroplasty.

In conclusion, this trial of thromboprophylaxis after total knee replacement found that rivaroxaban, an orally effective direct factor Xa inhibitor, given in a fixed, unmonitored, once-daily dose, was superior to enoxaparin in preventing venous thrombosis, with similar rates of bleeding. Rivaroxaban merits further investigation for its ability to prevent venous thrombosis.

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APPENDIX

The members of the RECORD3 study group were as follows: **Steering Committee** — M.R. Lassen (chair), W. Ageno, L.C. Borris, J.R. Lieberman, N. Rosencher, A.G.G. Turpie, and K. Harris and M. Lederman (nonvoting members); **Independent Central Adjudication Committee** — M. Levine; **Venous Thromboembolic Event Adjudication Committee** — H. Eriksson, G. Sandgren, J. Wallin; **Cardiovascular Adverse Event Adjudication Committee** — J.P. Bassand, C. Bode, T. Lüscher; **Bleeding Event Adjudication Committee** — U. Angeras, A. Falk, M. Prins; **Data and Safety Monitoring Board** — H. Bounameaux, S. Dittmar (sponsor contact), D. Larray, W. Lehmacher (independent statistician), A. Leizorovicz; **Sponsor, Bayer HealthCare** —A. Benson (statistical analysis); A. Duszczyszyn (study management); M. Lederman (medical expert). The RECORD3 investigators were as follows (with the numbers of patients enrolled at each site in parantheses): **Austria (89)** — J. Hochreiter, G. Labek, R. Windhager, P. Zenz; **Belgium (134)** — T. Borms, C. Brabants, P. Gunst, W. Henkes, H. Mortele, E. Vandermeersch, D. Vanlommel, B. Willems; **Canada (137)** — F. Abuzgaya, D. Armstrong, E. Dessouki, C. Dobson, S. Dolan, P. Grosso, G. Jasey, J. Naude, E. Wai, P. Zalzal; **China (162)** — T. Chen, H. Lv, Y. Wang, Q. Yang, B. Zeng, H. Zhang; **Colombia (100)** — B. Aguilera, R. Botero, A. Reyes; **Czech Republic (176)** — I. Kofranek, K. Koudela, M. Krbec, P. Kubat, J. Kubes, J. Sedivy, O. Stano, O. Vins; **Denmark (139)** — O.A. Borgwardt, P. Joergensen, M.R. Lassen, G. Lausten, S. Mikkelsen; **France (154)** — M. Carles, P. Chaussis, J.M. Debue, E. Eisenberg, C. Forestier, J.P. Franceschi, E. Gaertner, G. Hennion, T. Lazard, D. Lugrin, P. Macaire, X. Maschino, Y. Matuszczak, J.P. Moulinie, A. Peron; **Germany (190)** — W. Birkner, J. Eulert, H.M. Fritsche, A. Halder, T. Horacek, F. Kleinfeld, R. Krauspe, A. Kurth, P. Mouret, B. Muehlbauer, H. Schmelz; **Israel (143)** — V. Benkovich, B. Brenner, S. Dekel, M. Elias, N. Halperin, D. Hendel, U. Martinowitz, M. Nyska, I. Otremski; **Italy (179)** — B. Borghi, P. Cherubino, G. Davi, G. Della Rocca, G. Fanelli, P. Grossi, M. Gusso, R. Landolfi, R. Massei, G. Melis, R. Nardacchione, P. Parise; **Mexico (33)** — E. Berumen Nafarr, E. Gomez Sanchez, R. Inigo Pavlovich; **the Netherlands (139)** — C.N. Dijk, P.A. Nolte, H.M. Schuller, R. Slappendel, J.J.J. Van der List, C.C.P.M. Verheyen, H.M. Vis; **Norway (37)** — K. Al-Dekany, K. Griegel, R.E. Roenning, P. Stahl, O. Talsnes; **Peru (49)** — F. Arrieta, R. Cotrina, L. Merzthal, E. Pastor; **Poland (204)** — A. Bednarek, J. Blacha, A. Gusta, J. Kruczyski, K. Kwiatkowski, P. Madyk, S. Mazurkiewi, T. Niedwiedzki, J. Skowronski, M. Synder; **South Africa (143)** — U. Dhanjee, J. Diedericks, J. Engelbrecht, F. Greeff, B. Jacobson, S. Moodley, H. Myburgh, R. Routier, O. Van der Spuy, L. Van Zyl; **Spain (244)** — R. Canosa Sevillano, A. Delgado, J.L. Diaz Almodovar, F. Gomar, X. Granero, R. Lecumberri Villamedi, A. Navarro Quiles, R. Otero Fernandez, L. Peidro Garces, Á. Salvador; **Sweden (104)** — L. Ahnfelt, B. Edshage, B.I. Eriksson, M. Flondell, H. Laestander, S. Lind, B. Paulsson, A. Wykman.

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