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Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty

Bengt I. Eriksson, M.D., Ph.D., Lars C. Borris, M.D., Richard J. Friedman, M.D., Sylvia Haas, M.D., Menno V. Huisman, M.D., Ph.D., Ajay K. Kakkar, M.D., Ph.D., Tiemo J. Bandel, M.D., Horst Beckmann, Ph.D., Eva Muehlhofer, M.D., Frank Misselwitz, M.D., Ph.D., and William Geerts, M.D., for the RECORD1 Study Group*

ABSTRACT

BACKGROUND

This phase 3 trial compared the efficacy and safety of rivaroxaban, an oral direct inhibitor of factor Xa, with those of enoxaparin for extended thromboprophylaxis in patients undergoing total hip arthroplasty.

METHODS

In this randomized, double-blind study, we assigned 4541 patients to receive either 10 mg of oral rivaroxaban once daily, beginning after surgery, or 40 mg of enoxaparin subcutaneously once daily, beginning the evening before surgery, plus a placebo tablet or injection. The primary efficacy outcome was the composite of deep-vein thrombosis (either symptomatic or detected by bilateral venography if the patient was asymptomatic), nonfatal pulmonary embolism, or death from any cause at 36 days (range, 30 to 42). The main secondary efficacy outcome was major venous thromboembolism (proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism). The primary safety outcome was major bleeding.

RESULTS

A total of 3153 patients were included in the superiority analysis (after 1388 exclusions), and 4433 were included in the safety analysis (after 108 exclusions). The primary efficacy outcome occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group (absolute risk reduction, 2.6%; 95% confidence interval [CI], 1.5 to 3.7; P<0.001). Major venous thromboembolism occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group (absolute risk reduction, 1.7%; 95% CI, 1.0 to 2.5; P<0.001). Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin group (P=0.18).

CONCLUSIONS

A once-daily, 10-mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily, 40-mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. The two drugs had similar safety profiles. (ClinicalTrials.gov number, NCT00329628.)

From Sahlgrenska University Hospital–Östra, Gothenburg, Sweden (B.I.E.); Aarhus University Hospital, Aarhus, Denmark (L.C.B.); Medical University of South Carolina, Charleston (R.J.F.); Institute of Experimental Oncology and Therapy Research, Technical University of Munich, Munich, Germany (S.H.); Leiden University Medical Center, Leiden, the Netherlands (M.V.H.); Thrombosis Research Institute, and Barts and the London School of Medicine, London (A.K.K.); Bayer HealthCare, Wuppertal, Germany (T.J.B., H.B., E.M., F.M.); and University of Toronto, Toronto (W.G.). Address reprint requests to Dr. Eriksson at the Orthopedic Department, Sahlgrenska University Hospital–Östra, Smorslottsgatan 1, SE-41685 Gothenburg, Sweden, or at b.eriksson@orthop.gu.se.

*Members of the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (RECORD1) Study Group are listed in the Appendix.

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Prophylactic anticoagulant therapy is standard practice after total hip or knee arthroplasty, with a minimum recommended duration of 10 days.[1] After total hip arthroplasty, extended prophylaxis for 5 weeks after surgery reduces the incidence of symptomatic and asymptomatic venous thromboembolism more effectively than does short-term prophylaxis.[2] New deep-vein thromboses have been shown to form after the discontinuation of short-term prophylaxis.[3] Several meta-analyses suggest that extended thromboprophylaxis after total hip arthroplasty leads to a reduction in symptomatic venous thromboembolic events, without increasing the risk of major bleeding.[4-6] These findings led to a grade 1A recommendation for extended thromboprophylaxis after total hip arthroplasty in the guidelines of the American College of Chest Physicians.[1]

The current options for extended thromboprophylaxis are limited. Low-molecular-weight heparin preparations reduce thromboembolic events but need to be administered subcutaneously, and their cost-effectiveness has been shown only if patients or caregivers can be taught to inject the medication at home.[7,8] Vitamin K antagonists, such as warfarin, have unpredictable pharmacologic effects and numerous food and drug interactions, require frequent monitoring, and are therefore difficult to manage.[9] Furthermore, there is evidence to suggest that the incidence of major bleeding is greater with vitamin K antagonists than with low-molecular-weight heparin preparations given after total hip arthroplasty.[10]

Rivaroxaban is an oral direct inhibitor of factor Xa. The oral bioavailability of rivaroxaban is approximately 80%, and peak plasma concentrations are achieved in 2.5 to 4 hours.[11,12] Recent dose-finding studies in patients undergoing major orthopedic surgery showed a close correlation between the pharmacokinetic and pharmacodynamic effects of rivaroxaban and suggested that a 10-mg dose of rivaroxaban once daily was suitable for investigation in phase 3 trials.[13-17]

Our study, called Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (RECORD1), was a randomized, multinational, double-blind trial conducted to assess the efficacy and safety of a postoperative 10-mg oral dose of rivaroxaban given once daily as compared with a 40-mg subcutaneous dose of enoxaparin (a low-molecular-weight heparin), with the first dose given the evening before surgery and subsequent doses given once daily, for extended thromboprophylaxis after total hip arthroplasty.

METHODS

PATIENTS

Men and women of at least 18 years of age who were scheduled to undergo elective total hip arthroplasty were eligible for inclusion. Patients were ineligible if they were scheduled to undergo staged, bilateral hip arthroplasty, were pregnant or breast-feeding, had active bleeding or a high risk of bleeding, or had a contraindication for prophylaxis with enoxaparin or a condition that might require an adjusted dose of enoxaparin. Other ineligibility criteria were conditions preventing bilateral venography, substantial liver disease, severe renal impairment (creatinine clearance, <30 ml per minute), concomitant use of protease inhibitors for the treatment of human immunodeficiency virus infection, planned intermittent pneumatic compression, or a requirement for anticoagulant therapy that could not be stopped.

STUDY DESIGN AND DRUGS

Before surgery, patients were randomly assigned to a study group with the use of permuted blocks and stratification according to center by means of a central telephone system with a computer-generated randomization list. In a double-blind fashion, patients were assigned to receive either once-daily oral rivaroxaban in 10-mg tablets (Xarelto, Bayer HealthCare) or 40 mg of enoxaparin sodium administered by subcutaneous injection (Clexane/Lovenox, Sanofi-Aventis). Rivaroxaban was started 6 to 8 hours after wound closure. Enoxaparin was initiated 12 hours before surgery and restarted 6 to 8 hours after wound closure. Thereafter, study drugs were administered every 24 hours (range, 22 to 26) in the evening through day 35 (range, 31 to 39) after surgery (with the day of surgery defined as day 1). Patients also received placebo tablets or injections.

Patients underwent mandatory bilateral venography the day after the last dose of the study drug, at 36 days (range, 30 to 42). No further study medication was given after venography, although further thromboprophylaxis was continued at the investigator's discretion. Patients had a follow-up visit 30 to 35 days after the last dose of the study drug.

The trial was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board at each center, and written informed consent was obtained from all patients before randomization.

The study was designed and supervised by a steering committee. The data were collected and analyzed by the sponsors of the study, Bayer HealthCare and Johnson & Johnson. All authors contributed to the writing of the manuscript, had full access to all the data and analyses, and vouch for the accuracy and completeness of the data reported.

OUTCOME MEASURES

All outcomes were assessed by central independent adjudication committees whose members were unaware of the patients' study-group assignments. The primary efficacy outcome was the composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause up to 36 days (range, 30 to 42). The main secondary efficacy outcome was major venous thromboembolism, which was defined as the composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism. Other efficacy outcomes included the incidence of deep-vein thrombosis (any thrombosis, including both proximal and distal), the incidence of symptomatic venous thromboembolism during treatment and follow-up (30 to 35 days after the last dose of a study drug), and death during the follow-up period.

Deep-vein thrombosis was assessed at 36 days (range, 30 to 42) or earlier if the patient was symptomatic, by means of systematic ascending, bilateral venography with the use of the Rabinov and Paulin technique.[18] In cases of suspected pulmonary embolism, spiral computed tomography, perfusion–ventilation lung scintigraphy, or pulmonary angiography was performed, and the films or images were sent to the central adjudication committee. Autopsies were requested in the event of a patient's death.

The main safety outcome was the incidence of major bleeding beginning after the first dose of the study drug and up to 2 days after the last dose of the study drug (on-treatment period). Major bleeding was defined as bleeding that was fatal, occurred in a critical organ (e.g., retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or required reoperation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g per deciliter or that required transfusion of 2 or more units of whole blood or packed cells. Other safety outcomes included any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications (a composite of excessive wound hematoma and reported surgical-site bleeding), any bleeding that started after the first oral dose of rivaroxaban or placebo and ended up to 2 days after the last dose was administered, adverse events, and death.

During the study and at follow-up, laboratory variables, including liver enzymes, and cardiovascular events were monitored. Cardiovascular events occurring up to 1 calendar day after the cessation of the study drug were classified as on-treatment events.

STATISTICAL ANALYSIS

The aim of the trial was first to test the null hypothesis that the efficacy of rivaroxaban was inferior to that of enoxaparin in the per-protocol population. If noninferiority was shown, a second analysis would determine whether the efficacy of rivaroxaban was superior to that of enoxaparin in the modified intention-to-treat population.

The modified intention-to-treat analysis included patients who had undergone planned surgery, had taken a study drug, and had undergone an adequate assessment for thromboembolism. These patients were included in the per-protocol analysis, provided they had no major deviation from the protocol (for details, see Table 1). The safety analysis included patients who had received at least one dose of a study drug. Patients were included in the assessment for major venous thromboembolism if the proximal veins could be evaluated on venography, regardless of whether the distal veins could be evaluated.

The primary efficacy analysis was conducted for noninferiority in the per-protocol population and for superiority in the modified intention-to-treat population. The difference between the incidence rates in the rivaroxaban group and the enoxaparin group was estimated by stratification according to country, with the use of Mantel–Haenszel weighting with a corresponding asymptotic two-sided 95% confidence interval. Testing for noninferiority and testing for superiority were both based on the 95% confidence interval. The

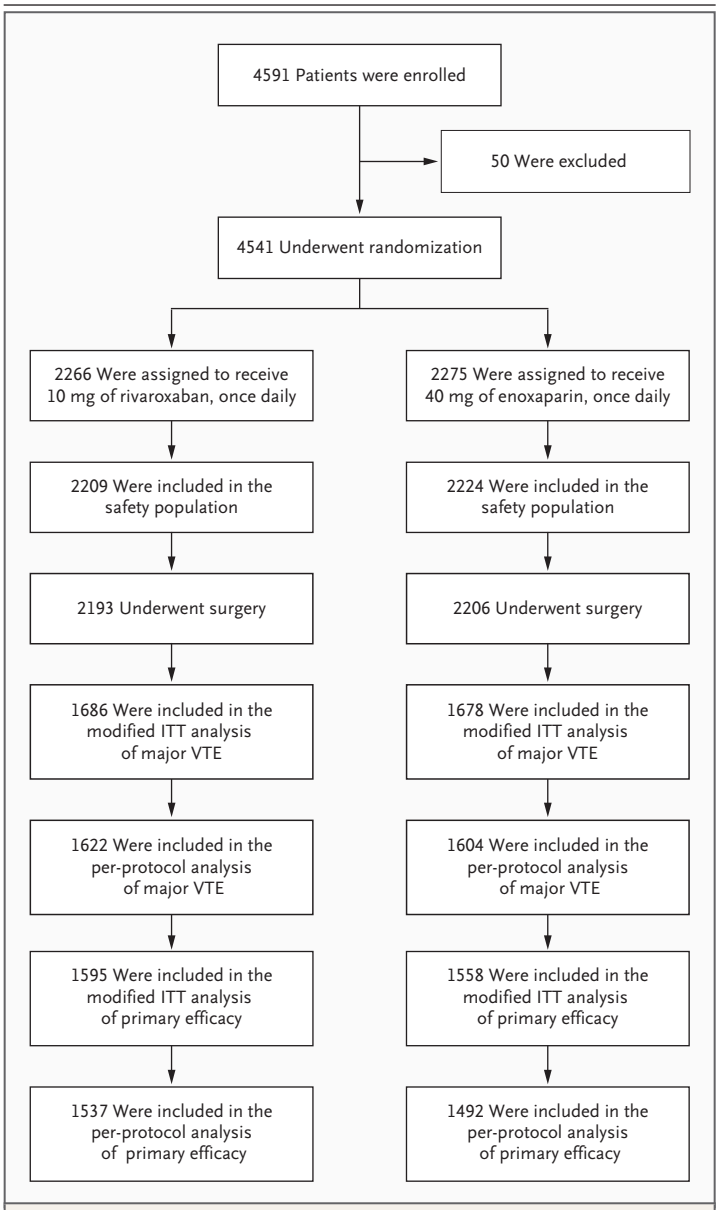

Figure 1. Enrollment and Outcomes.

Patients were included in the analysis of major venous thromboembolism (VTE) if proximal veins could be evaluated on venography, regardless of whether distal veins could be evaluated. Thus, patients in the modified intention-to-treat (ITT) analysis of primary efficacy are not a subgroup of those in the per-protocol analysis of major VTE.

threshold for the noninferiority test was an absolute margin of 3.5% for the primary efficacy outcome and an absolute margin of 1.5% for major venous thromboembolism.

The sample-size calculation was based on an assumed rate of 8% for the primary efficacy outcome with both study drugs and a noninferiority threshold of 3.5%. If these assumptions were correct, 1562 patients per study group would be sufficient to show noninferiority with a power of 95% and a one-sided type I error rate of 2.5%. It was assumed that 25% of patients would not have valid venograms, resulting in a target sample size of 4200 patients.

The analysis of the difference in the incidence of major bleeding between the study groups was performed in the same manner as that of efficacy; other safety outcomes were analyzed with the use of appropriate descriptive methods. For sex and other categorical variables, the two study groups were compared with the use of a Cochran–Mantel–Haenszel test, adjusted for country. For continuous variables, the groups were compared by analysis of variance. All reported P values are two-sided, with a type I error rate of 5%. No interim analyses were planned.

RESULTS

STUDY POPULATIONS

Between February 2006 and March 2007, a total of 4591 patients were enrolled in 27 countries worldwide (Fig. 1). A total of 3029 patients were included in the per-protocol population, and 3153 were included in the modified intention-to-treat population. The reasons for exclusion from the various analyses were similar between the two groups (Table 1). Demographic and surgical characteristics were also similar between the two groups (Table 2). The mean duration of prophylaxis was 33.4 days in the rivaroxaban group and 33.7 days in the enoxaparin group (safety population).

EFFICACY OUTCOMES

In the per-protocol population, the primary efficacy outcome occurred in 13 of 1537 patients (0.8%) in the rivaroxaban group and in 50 of 1492 patients (3.4%) in the enoxaparin group (weighted risk reduction in the rivaroxaban group, 2.5 percentage points; 95% confidence interval [CI], 1.5 to 3.6). This analysis showed the noninferiority of rivaroxaban, as compared with enoxaparin. In the modified intention-to-treat population, the primary efficacy outcome occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group (weighted risk reduction, 2.6 percentage points; 95% CI, 1.5 to 3.7; P<0.001; relative risk reduction, 70%; 95% CI, 49 to 82; P<0.001) (Table 3). This analysis showed

Table 1. Criteria for the Exclusion of Patients from Analyses.

Variable	Rivaroxaban	Enoxaparin
	no. (%)	
Underwent randomization	2266	2275
Did not receive a study drug	57 (2.5)	51 (2.2)
Included in safety analysis	2209 (97.5)	2224 (97.8)
Did not undergo planned surgery	17 (0.8)	21 (0.9)
No surgery	16 (0.7)	18 (0.8)
Not prespecified surgery	1 (<0.1)	3 (0.1)
Received wrong study drug	1 (<0.1)	2 (0.1)
Had inadequate assessment of thromboembolism	588 (25.9)	635 (27.9)
Venography not performed	319 (14.1)	322 (14.2)
Unilateral venography performed	105 (4.6)	105 (4.6)
Venographic findings indeterminate or could not be evaluated	121 (5.3)	164 (7.2)
Venography not performed by day 36±6	43 (1.9)	44 (1.9)
Inadequate evaluation of efficacy (source data not verified)	8 (0.4)	8 (0.4)
Included in modified intention-to-treat analysis of primary efficacy	1595 (70.4)	1558 (68.5)
Received first postoperative dose of study drug >24 hr after surgery	16 (0.7)	16 (0.7)
Assessment of venous thromboembolism outside time window*	20 (0.9)	26 (1.1)
Compliance <80%	16 (0.7)	16 (0.7)
Received wrong study drug	1 (<0.1)	1 (<0.1)
Received a prohibited anticoagulant	5 (0.2)	7 (0.3)
Included in per-protocol analysis of primary efficacy	1537 (67.8)	1492 (65.6)
Included in analysis of symptomatic venous thromboembolism (safety population of patients who underwent surgery)	2193 (96.8)	2206 (97.0)
Included in modified intention-to-treat analysis of major venous thromboembolism†	1686 (74.4)	1678 (73.8)
Included in per-protocol analysis of major venous thromboembolism†	1622 (71.6)	1604 (70.5)

* Assessment of venous thromboembolism was considered to be outside the time window if it was performed more than 36 hours after the last dose of a study drug for a positive result or more than 72 hours after the last dose of a study drug for a negative result.

† Patients were included in the analysis of major venous thromboembolism if proximal veins could be evaluated on venography, regardless of whether distal veins could be evaluated.

the superiority of rivaroxaban, as compared with enoxaparin.

In the per-protocol population, major venous thromboembolism occurred in 2 of 1622 patients (0.1%) in the rivaroxaban group and in 29 of 1604 patients (1.8%) in the enoxaparin group (weighted risk reduction in the rivaroxaban group, 1.7 percentage points; 95% CI, 1.0 to 2.4). This analysis showed the noninferiority of rivaroxaban, as compared with enoxaparin. In the modified intention-to-treat population, major venous thromboembolism occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group (weighted risk reduction, 1.7 percentage points; 95% CI, 1.0 to 2.5; P<0.001; relative risk reduction, 88%; 95% CI, 66 to 96; P<0.001) (Table 3). This analysis showed the superiority of rivaroxaban, as compared with enoxaparin.

The observed rates of symptomatic venous thromboembolism among patients undergoing surgery who were included in the safety analysis were similar in the rivaroxaban group and the enoxaparin group (0.3% and 0.5%, respectively) (Table 3). During the treatment period, there were four deaths in each group in the safety population (0.2%). On the basis of adjudication, in the rivaroxaban group, two deaths were possibly related

Table 2. Demographic and Clinical Characteristics of the Patients (Safety Population).

Characteristic	Rivaroxaban (N=2209)	Enoxaparin (N=2224)
Female sex — no. (%)	1220 (55.2)	1242 (55.8)
Age — yr		
Mean	63.1	63.3
Range	18–91	18–93
Weight — kg		
Mean	78.1	78.3
Range	37–159	40–132
Body-mass index*		
Mean	27.8	27.9
Range	16.2–53.4	15.2–50.2
Race or ethnic group — no. (%)†		
White	2041 (92.4)	2049 (92.1)
Hispanic	22 (1.0)	31 (1.4)
Black	20 (0.9)	19 (0.9)
Asian	5 (0.2)	2 (0.1)
Other or missing data	121 (5.5)	123 (5.5)
History of venous thromboembolism — no. (%)	47 (2.1)	55 (2.5)
Previous orthopedic surgery — no. (%)	490 (22.2)	500 (22.5)
Type of surgery — no. (%)		
Primary	2127 (96.3)	2118 (95.2)
Revision	66 (3.0)	86 (3.9)
No surgery or missing data	16 (0.7)	20 (0.9)
Use of cement — no. (%)	857 (38.8)	869 (39.1)
Type of anesthesia — no. (%)		
General only	661 (29.9)	648 (29.1)
General and regional	223 (10.1)	228 (10.3)
Regional only	1308 (59.2)	1330 (59.8)
Missing data	17 (0.8)	18 (0.8)
Duration of surgery — min		
Mean	90.6	91.3
Range	27–480	25–345

* The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race or ethnic group was assessed by investigators according to disclosure requirements in each country.

to venous thromboembolism, and two deaths were unrelated to venous thromboembolism; in the enoxaparin group, one death was related to venous thromboembolism, and three deaths were unrelated to venous thromboembolism. During the follow-up period, in the rivaroxaban group, one patient had symptomatic proximal deep-vein thrombosis and one patient died from causes unrelated to venous thromboembolism; in the enoxaparin group, three patients had symptomatic proximal deep-vein thrombosis and one patient had distal deep-vein thrombosis.

SAFETY OUTCOMES

Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) patients in the enoxaparin group (unweighted absolute increase in risk in the rivaroxaban group, 0.2%; 95% CI, −0.1 to 0.5) (Tables 4 and 5). In the rivaroxaban group, there was one fatal bleeding event, which occurred before the administration of the first dose of rivaroxaban, and one intraocular bleeding event, which resolved without discontinuation of rivaroxaban (Table 5). The combined incidence of major and clinically relevant nonmajor bleeding events was 3.2% (70 of 2209 patients) in the rivaroxaban group and 2.5% (56 of 2224 patients) in the enoxaparin group (weighted absolute increase in risk, 0.6%; 95% CI, −0.4 to 1.6). The incidence of hemorrhagic wound complications was similar in the two groups, occurring in 1.5% of patients in the rivaroxaban group and in 1.7% of patients in the enoxaparin group. The number of patients receiving blood transfusions and the median amount of blood in the postoperative drain were similar in the two groups, as was the incidence of all bleeding events (Table 4).

OTHER OBSERVATIONS

Rivaroxaban and enoxaparin were associated with a similar number of adverse events (Table 4; and Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). An on-treatment elevation in the plasma alanine aminotransferase level (i.e., a level of more than three times the upper limit of the normal range) occurred in 43 of 2128 patients (2.0%) in the rivaroxaban group, with all cases resolving by the end of the follow-up period, and in 57 of 2129 patients (2.7%) in the enoxaparin group, with all cases resolving by the end of the follow-up period (with no follow-up data available for 1 patient who withdrew from the study). One patient in each group had an elevated alanine aminotransferase level and a concomitant bilirubin level of more than twice the upper limit of the normal range. The

Table 3. Incidence of Efficacy Events (Modified Intention-to-Treat Population).

Outcome	Rivaroxaban		Enoxaparin		Absolute Risk Reduction*	P Value†
	no. with events/ total no.	*% (95% CI)*	*no. with events/ total no.*	*% (95% CI)*	*% (95% CI)*	
Primary efficacy outcome‡	18/1595	1.1 (0.7 to 1.8)	58/1558	3.7 (2.8 to 4.8)	–2.6 (–3.7 to –1.5)	<0.001
Major venous thromboembolism§	4/1686	0.2 (0.1 to 0.6)	33/1678	2.0 (1.4 to 2.8)	–1.7 (–2.5 to –1.0)	<0.001
Death during on-treatment period	4/1595	0.3 (0.1 to 0.6)	4/1558	0.3 (0.1 to 0.7)	0.0 (–0.4 to 0.4)	1.00
Nonfatal pulmonary embolism	4/1595	0.3 (0.1 to 0.6)	1/1558	0.1 (<0.1 to 0.4)	0.2 (–0.1 to 0.6)	0.37
Deep-vein thrombosis	12/1595	0.8 (0.4 to 1.3)	53/1558	3.4 (2.6 to 4.4)	–2.7 (–3.7 to –1.7)	<0.001
Proximal	1/1595	0.1 (<0.1 to 0.4)	31/1558	2.0 (1.4 to 2.8)	–1.9 (–2.7 to –1.2)	<0.001
Distal only	11/1595	0.7 (0.3 to 1.2)	22/1558	1.4 (0.9 to 2.1)	–0.7 (–1.5 to 0.0)	0.04
Symptomatic venous thromboembolism¶						
During treatment	6/2193	0.3 (0.1 to 0.6)	11/2206	0.5 (0.3 to 0.9)	–0.2 (–0.6 to 0.1)	0.22
During follow-up	1/2193	<0.1 (<0.1 to 0.3)	4/2206	0.2 (0.1 to 0.5)	–0.1 (–0.4 to 0.1)	0.37
Death during follow-up	1/1595	0.1 (<0.1 to 0.4)	0/1558	0.0 (0.0 to 0.2)	0.1 (–0.2 to 0.4)	1.00

* The absolute risk reduction, calculated with the use of a weighted Mantel–Haenszel test, is for patients receiving rivaroxaban, as compared with those receiving enoxaparin. For outcomes that occurred infrequently (i.e., fewer than 10 events in total, including death, pulmonary embolism, and symptomatic venous thromboembolism during follow-up), unweighted risk reductions and exact confidence intervals are given.

† Values were calculated on the basis of the Mantel–Haenszel weighted estimator. For outcomes that occurred infrequently (i.e., fewer than 10 events in total, including death, pulmonary embolism, and symptomatic venous thromboembolism during the follow-up period), the listed P values were calculated with the use of Fisher's exact test.

‡ The primary efficacy outcome was a composite of any deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause.

§ Major venous thromboembolism was a composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism.

¶ Symptomatic venous thromboembolism included any symptomatic deep-vein thrombosis (proximal or distal) and nonfatal or fatal symptomatic pulmonary embolism in patients in the safety population who had undergone surgery.

liver enzyme levels resolved with continued administration of rivaroxaban and with the discontinuation of enoxaparin, according to the prespecified criteria. During the entire study period, 13 cardiovascular events occurred in 11 patients in the rivaroxaban group, and 10 events occurred in 10 patients in the enoxaparin group. Of these cardiovascular events, on-treatment events occurred in five patients in the rivaroxaban group and in nine patients in the enoxaparin group; during follow-up, eight events occurred in seven patients in the rivaroxaban group, and one patient had an event in the enoxaparin group (Table 4).

DISCUSSION

This trial showed that oral, once-daily rivaroxaban has potential for extended thromboprophylaxis after total hip arthroplasty. Rivaroxaban was significantly more effective than enoxaparin for the prevention of venous thromboembolic events. Among patients receiving rivaroxaban, as compared with those receiving enoxaparin, there was an absolute risk reduction of 2.6% (relative risk reduction, 70%) for the primary efficacy outcome of deep-vein thrombosis, pulmonary embolism, or death from any cause and an absolute risk reduction of 1.7% (relative risk reduction, 88%) for major venous thromboembolism.

The superior efficacy of rivaroxaban was not associated with any significant increases in the incidence of major bleeding or any other bleeding events. The number of major bleeding events in this study was lower than that reported in several other studies,[19-21] which may be due, in part, to the difference in definitions of bleeding that were used in the various studies. Almost half the patients who undergo this type of surgical procedure require a transfusion of 2 or more units of blood.[15,16,22-24] In our study, the inclusion of a secondary bleeding outcome, hemorrhagic wound complication (which encompassed surgical-site

Table 4. Adverse Events (Safety Population).*

Event	Rivaroxaban (N=2209)	Enoxaparin (N=2224)	P Value
Any on-treatment bleeding — no. (%)†	133 (6.0)	131 (5.9)	0.94
Major bleeding			
No. of patients (%)	6 (0.3)	2 (0.1)	0.18
95% CI — %	0.1–0.6	<0.1–0.3	
Fatal bleeding — no. (%)	1 (<0.1)‡	0	
Bleeding into a critical organ — no. (%)	1 (<0.1)	0	
Bleeding leading to reoperation — no. (%)	2 (0.1)	1 (<0.1)	
Clinically overt extrasurgical-site bleeding — no. (%)			
Leading to a fall in hemoglobin	2 (0.1)	1 (<0.1)	
Leading to transfusion of ≥2 units of blood	2 (0.1)	1 (<0.1)	
Nonmajor bleeding — no. (%)	128 (5.8)	129 (5.8)	
Clinically relevant	65 (2.9)	54 (2.4)	
Hemorrhagic wound complication (composite of excessive wound hematoma and reported surgical-site bleeding)	34 (1.5)	38 (1.7)	
Other nonmajor bleeding	71 (3.2)	77 (3.5)	
Postoperative wound infection — no. (%)§	8 (0.4)	8 (0.4)	
Any bleeding beginning after first rivaroxaban or placebo tablet — no./total no. (%)¶	119/2183 (5.5)	109/2198 (5.0)	
Patients receiving blood transfusions — no. (%)	1210 (54.8)	1249 (56.2)	
Volume of blood transfusion in patients who had transfusions — ml			
Median	568	585	
Range	50–3577	20–6561	
Patients with postoperative drain — no. (%)	1833 (83.0)	1849 (83.1)	
Volume in drain in patients for whom data were available — ml			
Median	540	530	
Range	6–5180	2–3490	
Any on-treatment adverse event — no. (%)	1413 (64.0)	1439 (64.7)	
Drug-related adverse event — no. (%)	270 (12.2)	265 (11.9)	
Cardiovascular event — no. (%)			
During on-treatment period‖	5 (0.2)	9 (0.4)	
Death	1 (<0.1)	0	
Ischemic stroke	1 (<0.1)	3 (0.1)	
Myocardial infarction	3 (0.1)	6 (0.3)	
During follow-up**	7 (0.3)	1 (<0.1)	
Death	2 (<0.1)††	1 (<0.1)	
Ischemic stroke	2 (<0.1)‡‡	0	
Myocardial infarction	4 (0.2)‡‡	0	

* Patients could have more than one event, and an event could fall into more than one category.
† Adjudicated on-treatment bleeding events included those beginning after the initiation of the study drug and up to 2 days after the last dose of the study drug.
‡ The event occurred before the administration of the first dose of rivaroxaban.
§ The definition for this event is listed in the *Medical Dictionary for Regulatory Activities*.
¶ Adjudicated on-treatment bleeding events beginning after the first rivaroxaban or placebo tablet were those that occurred up to 2 days after the last dose of the study drug. The denominator is the number of patients in the safety population who received at least one tablet of rivaroxaban or placebo.
‖ On-treatment events occurred up to 1 calendar day after the last dose of the study drug.
** Events during follow-up occurred more than 1 calendar day after the last dose of the study drug.
†† One patient also had an on-treatment cardiovascular event.
‡‡ One patient had both an ischemic stroke and a myocardial infarction during follow-up.

Table 5. On-Treatment Major Bleeding Events (Safety Population).

Variable	No.	Site	Timing	Details
Rivaroxaban				
Major bleeding	6			
Fatal bleeding	1	Surgical	During surgery	No rivaroxaban had been given
Bleeding into a critical organ	1	Intraocular	Day of surgery	Patient had Gaucher's disease and a history of intraocular bleeding
Bleeding leading to reoperation	2			
First patient		Surgical	Day of surgery	Reoperation was wound revision due to serosanguineous drainage
Second patient		Surgical	17 Days after surgery	Reoperation for hematoma
Clinically overt extrasurgical-site bleeding leading to a fall in hemoglobin and transfusion of ≥2 units of blood	2			
First patient		Gastrointestinal	2 Days after surgery	"Coffee-ground" vomiting; patient had a history of peptic ulcer disease; rivaroxaban was discontinued
Second patient		Gastrointestinal	21 Days after surgery	Gastrointestinal bleeding requiring transfusion of 2 units of blood; endoscopy showed gastropathy consistent with the use of nonsteroidal antiinflammatory drugs
Enoxaparin				
Major bleeding	2			
Bleeding leading to reoperation	1	Surgical	Day of surgery	Arterial bleeding; wound revision was performed; enoxaparin was discontinued
Clinically overt extrasurgical-site bleeding leading to a fall in hemoglobin and transfusion of ≥2 units of blood	1	Gastrointestinal	13 Days after surgery	Melena diagnosed as bleeding in the upper gastrointestinal tract; patient recovered within 1 day; enoxaparin was discontinued

bleeding and excessive wound hematoma), allowed such events to be reported, and there was no significant difference in bleeding outcomes between the two groups. There were similar incidences of elevated liver enzyme levels in the two groups during the 5-week on-treatment period.

As in most other phase 3 clinical trials of thromboprophylaxis in orthopedic patients, the patients who were included in the efficacy analysis did not include those who did not undergo an adequate assessment (i.e., venography) for the presence or absence of deep-vein thrombosis.[25,26] In our study, 67% of the patients were included in the per-protocol population. Because the number of valid venograms was smaller than expected, the steering committee increased the recruitment of patients beyond the planned 4200 patients to more than 4500 patients to maintain the statistical power of the trial.

Several sensitivity analyses were performed to ensure that missing data did not affect the power of the trial or bias the outcome. These analyses supported the main finding of the study that there was a significant reduction in the incidence of the primary outcome in patients receiving rivaroxaban, as compared with those receiving enoxaparin. When all adjudicated events — positive results on venography, symptomatic events, and deaths — and all venograms that were adjudicated to show no deep-vein thrombosis were considered (regardless of whether they occurred outside the predefined time windows), the weighted absolute risk reduction for the primary outcome in the rivaroxaban group, as compared with the enoxaparin group, was 2.7% (95% CI, 1.6 to 3.8). Furthermore, in cases in which the assessment of the central adjudication committee was not clear and all available assessments by investiga-

tors were included in addition to the above analysis, the weighted absolute risk reduction was 3.0% (95% CI, 1.8 to 4.1) in the rivaroxaban group, as compared with the enoxaparin group. Thus, our study showed that extended thromboprophylaxis with 10 mg of rivaroxaban once daily for 5 weeks resulted in a very low incidence of thrombosis, with a safety profile similar to that of enoxaparin.

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APPENDIX

The members of the RECORD1 Study Group were the following: **Steering Committee:** B.I. Eriksson (chair, Sweden), L.C. Borris (Denmark), R.J. Friedman (United States), W. Geerts (Canada), S. Haas (Germany), M.V. Huisman (the Netherlands), A.K. Kakkar (United Kingdom), E. Muehlhofer (Germany); **Independent Central Adjudication Committee:** M. Levine (Canada) on behalf of the committee; **Venous Thromboembolic Event Adjudication Committee:** H. Eriksson (Sweden), G. Sandrgen (Sweden), J. Wallin (Sweden); **Cardiovascular Adverse Event Adjudication Committee:** C. Bode (chair, Germany), J.P. Bassand (France), T. Lüscher (Switzerland); **Bleeding Event Adjudication Committee:** U. Angeras (Sweden), A. Falk (Sweden), M. Prins (the Netherlands); **Data and Safety Monitoring Board:** A. Leizorovicz (chair, France), H. Bounameaux (Switzerland), D. Larrey (France); **Bayer HealthCare, Germany**: *Study Management:* A. Migge; *Statistical Analysis:* H. Beckmann; *Medical Expert*: E. Muehlhofer.

Investigators: Argentina (91 patients) — H. Caviglia, J. Ceresetto, A. Cicchetti, A. D'Onofrio, A. Diaz, H. Mendler, J. Saa; **Australia (73 patients)** — P. Blombery, B. Chong, A. Gallus, M. Leahy, H. Salem; **Austria (305 patients)** — N. Bauer, N. Boehl, N. Freund, J. Hochreiter, M. Jakubek, G. Labek, R. Windhager, P. Zenz; **Belgium (217 patients)** — T. Borms, C. Brabants, J. Colinet, J. de Rycke, R. Driesen, P. Gunst, H. Mortele, L. van Loon, E. Vandermeersch, D. Vanlommel; **Brazil (118 patients)** — R. Dantas Queiroz, M. Fridman, J. Mezzalira Penedo, C. Schwartsmann; **Canada (139 patients)** — F. Abuzgaya, E. Belzile, C. Dobson, W. Fisher, P. Grosso, M. Mant, R. Pototschnik, S. Solymoss, P. Zalzal; **Chile (18 patients)** — S. Bittelman, M. Cordova; **Colombia (48 patients)** — A. Reyes, C. Rocha, D. Toledo; **Czech Republic (278 patients)** — J. Altschul, J. Fousek, K. Koudela, Z. Kriz, M. Lutonsky, M. Pach, P. Sedivy, J. Stehlik, M. Svagr, M. Svec; **Denmark (150 patients)** — O.A. Borgwardt, P. Joergensen, M.R. Lassen, G. Lausten, S. Mikkelsen; **Finland (115 patients)** — P. Jokipii, M. Pesola, P. Waris; **France (235 patients)** — J.M. Debue, C. Forestier, G. Hennion, T. Lazard, P. Macaire, J.Y. Maire, A. Marouan, X. Maschino, Y. Matuszczak, J.P. Moulinie, M. Osman, A. Peron, J.J. Pinson; **Germany (311 patients)** — W. Birkner, M. Buechler, J. Eulert, H.M. Fritsche, K.P. Guen, A. Halder, T. Horacek, A. Kiekenbeck, F. Kleinfeld, R. Krauspe, A. Kurth, K. Labs, W. Mittelme, P. Mouret, B. Muehlbauer, M. Quante, H. Schmelz, T. Wirth; **Greece (30 patients)** — G. Babis, A. Beldekos, P. Soukakos; **Hungary (272 patients)** — L. Bucsi, E. Lenart, G. Mike, A. Sarvary, F. Shafiei, A. Szenbeni, M. Szendroi, J. Toth, K. Toth; **Israel (117 patients)** — V. Benkovich, B. Brenner, S. Dekel, N. Halperin, D. Hendel, U. Martinovich, M. Nyska, M. Salai; **Italy (304 patients)** — B. Borghi, M. Bosco, C. Castelli, P. Cherubino, F. Franchin, G. Fraschini, F. Greco, P. Grossi, M. Gusso, R. Landolfi, T. Leali, C. Lodigiani, E. Marinoni, U. Martorana, L. Massari, G. Melis, A. Miletto, P. Parise, G. Rinaldi, R. Riva, M. Silingardi; **Lithuania (128 patients)** — N. Porvaneckas, A. Smailys; **the Netherlands (199 patients)** — 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 (89 patients)** — O. Aarseth, K. Al-Dekany, P. Borgen, R.E. Roenning, O. Talsnes; **Poland (702 patients)** — A. Bednarek, J. Blacha, J. Deszczyski, J. Dutka, T. Gazdzik, E. Golec, A. Gorecki, A. Gusta, M. Krasicki, J. Kruczyski, D. Kusz, K. Kwiatkowsk, S. Mazurkiewi, T. Niedwiedzki, A. Pozowski, J. Skowronski, R. Swaton, M. Synder, T. Tkaczyk; **Slovakia (54 patients)** — L. Knapec, M. Lisy, I. Stasko; **South Africa (51 patients)** — J. Engelbrecht, H. Myburgh, L. van Zyl; **Spain (201 patients)** — R. Canosa Sevillano, A. Delgado, J.L. Diaz Almodovar, J. Giros Torres, X. Granero, F. Gomar, R. Lecumberri Villamedi, A. Navarro Quiles, R. Otero Fernandez, J. Paz Jimenez, L. Peidro Garces, J. Pino Minguez, L. Puig Verdier, A. Ruiz Sanchez, Á. Salvador, J.C. Valdes Casas; **Sweden (86 patients)** — B.I. Eriksson, H. Laestander, J. Liliequist, S. Lind, B. Paulsson, A. Wykman; **Turkey (80 patients)** — F. Altintas, T. Esemelli, V. Karatosun, E. Togrul, R. Tozun; **United States (180 patients)** — D. Allmacher, C. Buettner, C. Colwell, Jr., R. Friedman, J. Gimbel, M. Jove, R. King, K. Martin, R. Murray, P. Peters, Jr., S. Sledge, J. Swappach, O. Taunton, Jr., J. Ward.

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