ORIGINAL ARTICLE

Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery

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ABSTRACT

BACKGROUND

Nonmajor orthopedic surgery of the lower limbs that results in transient reduced mobility places patients at risk for venous thromboembolism. Rivaroxaban may be noninferior to enoxaparin with regard to the prevention of major venous thromboembolism in these patients.

METHODS

In this international, parallel-group, randomized, double-blind, noninferiority trial, we randomly assigned adult patients undergoing lower-limb nonmajor orthopedic surgery who were considered to be at risk for venous thromboembolism on the basis of the investigator's judgment to receive either rivaroxaban or enoxaparin. The primary efficacy outcome of major venous thromboembolism was a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death during the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment. A test for superiority was planned if rivaroxaban proved to be noninferior to enoxaparin. For all outcomes, multiple imputation was used to account for missing data. Prespecified safety outcomes included major bleeding (fatal, critical, or clinically overt bleeding or bleeding at the surgical site leading to intervention) and nonmajor clinically relevant bleeding.

RESULTS

A total of 3604 patients underwent randomization; 1809 patients were assigned to receive rivaroxaban, and 1795 to receive enoxaparin. Major venous thromboembolism occurred in 4 of 1661 patients (0.2%) in the rivaroxaban group and in 18 of 1640 patients (1.1%) in the enoxaparin group (risk ratio with multiple imputation, 0.25; 95% confidence interval, 0.09 to 0.75; $P<0.001$ for noninferiority; $P=0.01$ for superiority). The incidence of bleeding did not differ significantly between the rivaroxaban group and the enoxaparin group (1.1% and 1.0%, respectively, for major bleeding or nonmajor clinically relevant bleeding; 0.6% and 0.7%, respectively, for major bleeding).

CONCLUSIONS

Rivaroxaban was more effective than enoxaparin in the prevention of venous thromboembolic events during a period of immobilization after nonmajor orthopedic surgery of the lower limbs. (Funded by Centre Hospitalier Universitaire de Saint-Etienne and Bayer; PRONOMOS ClinicalTrials.gov number, NCT02401594.)

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The risk of venous thromboembolism — encompassing deep-vein thrombosis and pulmonary embolism — after major orthopedic surgery is high and is associated with long-term complications, functional disability, and death.[1] Clinical guidelines therefore recommend anticoagulant thromboprophylaxis after total hip or knee replacement or hip-fracture surgery to reduce the risk of a thrombotic event.[2]

Nonmajor orthopedic surgery of the lower limbs (i.e., excluding total hip or knee replacement or hip-fracture surgery) that results in transient reduced mobility also involves a risk of major venous thromboembolism of approximately 3% without prophylaxis in patients who have a distal lower-limb injury or undergo knee arthroscopy.[3] This risk increases with patient-related risk factors, including coexisting medical conditions, age, obesity, previous venous thromboembolism, medications, pregnancy or the postpartum state, and procoagulant changes after surgery.[4,5]

There is a lack of consensus on the use of thromboprophylaxis in patients undergoing nonmajor orthopedic surgery. In the United States, routine mechanical (nonpharmacologic) or pharmacologic prophylaxis is not required because U.S. guidelines assert that the risk of venous thromboembolism after such surgery is low.[6] European guidelines, however, recommend a personalized strategy of prophylaxis with low-molecular-weight heparin in patients who have one or more risk factors and whose risk of a thrombotic event exceeds that of a bleeding event.[4,7,8] Consequently, thromboprophylaxis after nonmajor orthopedic surgery remains a standard of care in many European countries.

As compared with enoxaparin therapy, treatment with the factor Xa inhibitor rivaroxaban results in a lower risk of a composite of symptomatic venous thromboembolism and death from any cause after elective total knee or hip replacement[9] and is indicated in those contexts.[10] We conducted the Prophylaxis in Nonmajor Orthopaedic Surgery (PRONOMOS) trial to compare the effect of rivaroxaban with that of enoxaparin in the prevention of major venous thromboembolism after lower-limb nonmajor orthopedic surgery.

METHODS

TRIAL DESIGN

In this international, parallel-group, randomized, double-blind, noninferiority trial, we compared rivaroxaban with enoxaparin in patients undergoing nonmajor orthopedic surgery in a lower limb. The trial was sponsored by Centre Hospitalier Universitaire de Saint-Etienne, France, and by Bayer. The protocol (including the statistical analysis plan), available with the full text of this article at NEJM.org, was developed by the authors and approved by the relevant regulatory authorities and ethics committees. The steering committee had overall scientific responsibility for the trial, which was managed by the contract research organization PSNResearch. An independent data and safety monitoring committee monitored the safety and efficacy data. Analyses were performed independently by the academic statistician. Bayer had no role in the design or conduct of the trial; the collection, management, analysis, or interpretation of the data; the preparation or approval of the manuscript; or the decision to submit the manuscript for publication. Medical writing assistance was funded by Centre Hospitalier Universitaire de Saint-Etienne. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Adults who had been admitted to the hospital to undergo nonmajor orthopedic surgery in the lower limbs and were to receive thromboprophylaxis for at least 2 weeks (according to the investigator's assessment of the patient's venous thromboembolic risk) were eligible for enrollment in the trial. Types of surgery included Achilles' tendon repair; knee surgery (including unicompartmental knee prosthesis); surgery involving the tibial plateau or femur (excluding femoral head or neck fractures); tibial or ankle fractures or tibial osteotomy; tibial tuberosity transposition; arthrodesis of the knee, ankle, or hindfoot; ligament repair of the knee with a planned immobilization or partial weight bearing; ligament repair of the ankle; or any elective orthopedic lower-limb surgery necessitating the use of thromboprophylaxis for more than 2 weeks. The enrollment criteria are described in the Supplementary Appendix, available at NEJM.org. All the participants provided written informed consent.

PROCEDURES

Prerandomization treatment with low-molecular-weight heparin was allowed for a maximum of 48 hours before surgery (maximum of one dose

per 24 hours). Randomization (in randomly permuted blocks of four) was conducted within 10 hours after surgery and was performed centrally in a 1:1 ratio with the use of an interactive Web-response system (ClinInfo) that assigned a unique randomization number to each eligible patient. Randomization was stratified according to center and intended treatment duration (2 weeks to 1 month, >1 month to 2 months, or >2 months). The intended duration of treatment was based on medical judgment and corresponded to the planned duration of immobilization (plaster cast or no-weight-bearing recommendation or partial weight bearing) and country-specific recommendations for the prevention of venous thromboembolism in adults undergoing orthopedic surgery.[2,4]

Patients who were randomly assigned to the rivaroxaban group were to receive 10 mg of rivaroxaban orally and a subcutaneous injection of placebo (in lieu of enoxaparin); patients who were randomly assigned to the enoxaparin group were to receive a subcutaneous injection of enoxaparin (at a dose of 40 mg [4000 IU of anti-Xa activity] in 0.4 ml of diluent) and an oral tablet of placebo (in lieu of rivaroxaban) (Fig. S1 in the Supplementary Appendix). The trial drug and matching placebo were administered once daily every 24 hours within a window of ±2 hours. Provided that hemostasis had been established, the first dose of the trial drug was administered between 6 and 10 hours after surgery if it could be given before 10 p.m. and at least 24 hours after any preoperative administration of low-molecular-weight heparin. If the first dose could not be given by 10 p.m., one postoperative dose of low-molecular-weight heparin was allowed, and administration of the first dose of the trial drug was postponed until the following day. Lists of concomitant medications that were, or were not, permitted during the trial are provided in the Supplementary Appendix.

At discharge, patients were provided with sufficient trial drugs for the intended treatment duration (i.e., until the end of immobilization). All the patients underwent systematic compression ultrasonography at the end of immobilization (i.e., between 15 days and 3 months after randomization) in order to detect asymptomatic proximal deep-vein thrombosis (see the Compression Ultrasonography Assessment section in the Supplementary Appendix). Patients were contacted by telephone 30 days (within a window of ±7 days) after the end of treatment to evaluate the occurrence of venous thromboembolic events.

Symptomatic venous thromboembolic events had to be confirmed by objective tests — that is, compression ultrasonography for deep-vein thrombosis and computed tomographic pulmonary angiography, ventilation–perfusion lung scanning, or pulmonary angiography for pulmonary embolism. Fatal pulmonary embolism was confirmed by means of autopsy or was imputed in cases of unexplained death when pulmonary embolism could not be ruled out.

OUTCOMES

The primary efficacy outcome of major venous thromboembolism was a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death during the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment. Prespecified secondary outcomes were safety outcomes of major bleeding (fatal, critical, or clinically overt bleeding or bleeding at the surgical site leading to intervention[11]), nonmajor clinically relevant bleeding, overt thrombocytopenia, and death from any cause. Full definitions are provided in the End Points section in the Supplementary Appendix. All suspected thrombotic or bleeding events and deaths were adjudicated by a central independent committee whose members were unaware of the treatment assignments. An additional post hoc analysis compared the composite of venous thromboembolism or major bleeding between groups (referred to as "net clinical benefit").

STATISTICAL ANALYSIS

To determine the noninferiority of rivaroxaban to enoxaparin, the primary analysis was performed in the intention-to-treat population (all the patients who underwent randomization) and in the per-protocol population (all patients meeting the inclusion criteria who underwent surgery, received at least one dose of trial medication, and had no major protocol violations). In the primary intention-to-treat analysis, we used multiple imputation to account for missing data as described in the Supplementary Appendix. The risk ratio and its 95% confidence interval were estimated with the use of a logistic-regression model. The non-

inferiority margin for the upper limit of the 95% confidence interval of the risk ratio comparing rivaroxaban with enoxaparin was set at 1.30. We estimated that a sample of 4400 patients would provide the trial with 90% power to show noninferiority at a two-sided type I error rate of 5% (see the Supplementary Appendix).

The protocol specified that, if noninferiority was shown for the primary outcome, a superiority test would then be performed. To show superiority, a two-sided Fisher's exact test at the 5% significance level was performed, and the resulting P value reported. Kaplan–Meier curves were constructed.

The risk ratio for the incidence of bleeding and other outcomes between the rivaroxaban group and the enoxaparin group was analyzed with the use of the same methods and population as for the primary analysis. Confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). Graphs were constructed with the use of R software, version 3.6.0. Further details on the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From December 8, 2015, to April 11, 2018, a total of 3604 patients underwent randomization at 200 sites in 10 countries. A total of 1809 patients were randomly assigned to receive rivaroxaban and 1795 to receive enoxaparin (Fig. S2). Across the trial sites, the median number of patients per site was 14 (interquartile range, 5 to 31; range, 1 to 272).

Although the aim was to enroll 4400 patients, slower-than-expected recruitment led to trial drugs reaching their expiration dates, with prohibitively high replacement costs. On these grounds, the steering committee and sponsors, who were unaware of any trial results, decided to stop enrollment in April 2018. The intended duration of treatment was 2 weeks to 1 month in 2152 patients (59.7%), more than 1 month to 2 months in 1351 patients (37.5%), and more than 2 months in 101 patients (2.8%). At the time of randomization, the characteristics of the two groups were well balanced (Table 1).

TREATMENT AND FOLLOW-UP

A prophylactic dose of low-molecular-weight heparin was given before surgery to 499 of 3604 patients (13.8%). The most frequent types of surgery were ligament repair of the knee (in 37.0% of patients), ankle fracture (15.1%), complicated knee arthroscopy (9.0%), tibial osteotomy (6.4%), tibial fracture (5.3%), and Achilles' tendon repair (5.1%). Neuraxial anesthesia was used in 47.1% of the patients, general anesthesia in 37.7%, peripheral-nerve block in 9.1%, and combined anesthesia in 6.2%. (Details are provided in Tables S1 and S2.)

The mean (±SD) duration of trial-drug administration was 28.6±14.3 days. (The intended and actual treatment durations are shown in Table S3.) The trial drug was temporarily discontinued in 2 patients (0.1%), both of whom were in the enoxaparin group, and permanently discontinued in 145 of 3504 patients (4.1%) overall, including 63 of 1760 (3.6%) in the rivaroxaban group and 82 of 1744 (4.7%) in the enoxaparin group. The mean number of unused tablets per patient (3.6±5.9 in the rivaroxaban group and 3.6±6.5 in the enoxaparin group) and of unused syringes per patient (3.5±5.9 and 3.6±6.5, respectively) was similar in the two treatment groups (Table S4).

The median follow-up was 59 days (interquartile range, 47 to 72) in the rivaroxaban group and 59 days (interquartile range, 47 to 73) in the enoxaparin group. The median follow-up after the end of treatment was 33 days (interquartile range, 31 to 34) in the rivaroxaban group and 33 days (interquartile range, 31 to 35) in the enoxaparin group. A total of 111 patients (3.1%) withdrew from the trial prematurely; a further 192 patients who were alive at the time of the intended date of compression ultrasonography did not undergo that evaluation. Overall, 303 patients (8.4%) had an incomplete assessment or no assessment of the primary outcome.

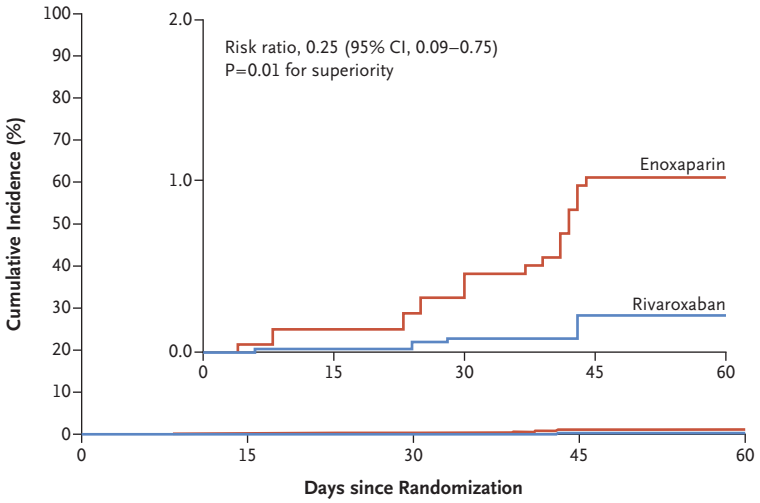
PRIMARY EFFICACY OUTCOME

The primary composite outcome occurred in 4 of 1661 patients (0.2%) in the rivaroxaban group and in 18 of 1640 patients (1.1%) in the enoxaparin group (risk ratio with multiple imputation, 0.25; 95% confidence interval [CI], 0.09 to 0.75; P<0.001 for noninferiority; P=0.01 for superior-

Table 1. Demographic and Baseline Characteristics of the Patients and Treatment Duration.*

Characteristic	Rivaroxaban (N=1809)	Enoxaparin (N=1795)
Median age (interquartile range) — yr	41 (29–54)	41 (29–54)
Male sex — no. (%)	1194 (66.0)	1149 (64.0)
Median body-mass index (interquartile range)†	26.3 (23.7–29.4)	26.3 (23.6–29.3)
Laboratory tests		
Platelets		
No. of patients with data	1350	1337
Median (interquartile range) — $\times 10^{-3}/mm^3$	241 (209–283)	238 (206–277)
Hemoglobin		
No. of patients with data	1351	1338
Median (interquartile range) — g/dl	14.6 (13.6–15.5)	14.6 (13.6–15.4)
Serum creatinine		
No. of patients with data	1554	1545
Median (interquartile range) — mg/dl	0.87 (0.75–1.00)	0.87 (0.76–1.00)
Creatinine clearance — no./total no. (%)		
30 to <50 ml/min	6/1554 (0.4)	14/1545 (0.9)
50 to <90 ml/min	248/1554 (16.0)	247/1545 (16.0)
≥90 ml/min	1300/1554 (83.7)	1284/1545 (83.1)
Medical history — no./total no. (%)		
Trauma	446/1793 (24.9)	497/1782 (27.9)
Diabetes	80/1799 (4.4)	62/1786 (3.5)
Coronary artery disease	52/1795 (2.9)	48/1786 (2.7)
Oral contraception or hormone therapy	46/1790 (2.6)	49/1778 (2.8)
Immobilization in the past 10 days	18/1799 (1.0)	21/1788 (1.2)
Venous thromboembolism	20/1797 (1.1)	14/1783 (0.8)
Respiratory failure	20/1799 (1.1)	13/1785 (0.7)
Stroke or transient ischemic attack	16/1798 (0.9)	11/1785 (0.6)
Hepatic disease	9/1799 (0.5)	21/1784 (1.2)
Gastrointestinal bleeding	4/1799 (0.2)	5/1786 (0.3)
Active cancer	3/1799 (0.2)	5/1786 (0.3)
Renal failure	2/1799 (0.1)	2/1785 (0.1)
Aspirin — no./total no. (%)	27/1618 (1.7)	21/1621 (1.3)
Intended treatment duration — no. (%)		
2 Wk to 1 mo	1082 (59.8)	1070 (59.6)
>1 Mo to 2 mo	677 (37.4)	674 (37.5)
>2 Mo	50 (2.8)	51 (2.8)

* Percentages may not total 100 because of rounding. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for creatinine clearance (as assessed by the Cockcroft–Gault formula) to milliliters per second per square meter of body-surface area, multiply by 0.02.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.



No. at Risk, According to Intended Treatment Period					
2 Wk to 1 mo					
Enoxaparin	1070	636	15	5	—
Rivaroxaban	1082	679	16	5	—
>1 Mo to 2 mo					
Enoxaparin	674	639	604	79	4
Rivaroxaban	677	644	617	78	7
>2 Mo					
Enoxaparin	51	45	44	42	34
Rivaroxaban	50	48	47	47	41

Figure 1. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

The primary efficacy outcome was a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death throughout the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment. The analysis was conducted in the intention-to-treat population (all the patients who underwent randomization). The inset shows the same data on an expanded y axis. Data for patients with missing compression ultrasonographic information were censored at the date of the most recent available follow-up information. Patients without an event at the end of their intended treatment period were no longer followed for events in this analysis and were subtracted from the number of patients at risk.

ity) (Fig. 1 and Table 2). The distribution of these events stratified according to the intended duration of thromboprophylaxis is provided in Table 2. Among the components of the primary outcome, there was a lower risk of symptomatic venous thromboembolic events in the rivaroxaban group than in the enoxaparin group (risk ratio with multiple imputation, 0.28; 95% CI, 0.08 to 1.00) (Table 2). The median time to an event was 26.0 days (interquartile range, 15.0 to 35.5) in the rivaroxaban group and 40.0 days (interquartile range, 25.0 to 42.0) in the enoxaparin group.

A sensitivity analysis was performed in which the risk observed in the enoxaparin group was applied to patients with missing information in the rivaroxaban group and a risk of zero was applied to patients with missing information in the enoxaparin group; the results were similar to those in the primary analysis (risk ratio, 0.33; 95% CI, 0.13 to 0.83). The primary efficacy results in the per-protocol analysis were also similar to those in the intention-to-treat analysis (Table S6). Selected prespecified subgroup analyses of the primary efficacy outcome are provided in Figure 2. Telephone follow-up, which occurred 30 days after treatment was stopped (within a window of ±7 days), showed that an additional 5 patients in the rivaroxaban group had received a diagnosis of deep-vein thrombosis and an additional 10 patients in the enoxaparin group had received a diagnosis of deep-vein thrombosis (in 9 patients) or pulmonary embolism (in 1).

Table 2. Primary Outcome of Venous Thromboembolism (Fatal or Nonfatal).

Outcome	Rivaroxaban (N=1809)	Enoxaparin (N=1795)	Risk Ratio (95% CI)*
	no. of patients with event/total no. of patients (%)		
Venous thromboembolism	4/1661 (0.2)	18/1640 (1.1)	0.25 (0.09–0.75)
Primary outcome, stratified according to intended duration of thromboprophylaxis			
2 Wk to 1 mo	2/1016 (0.2)	3/993 (0.3)	—
>1 Mo to 2 mo	2/599 (0.3)	15/605 (2.5)	—
>2 Mo	0/46	0/42	—
Components of the primary outcome			
Symptomatic venous thromboembolism	3/1756 (0.2)	11/1737 (0.6)	0.28 (0.08–1.00)
Distal deep-vein thrombosis†	3/1756 (0.2)	5/1737 (0.3)	—
Proximal deep-vein thrombosis†	0/1756	5/1737 (0.3)	—
Pulmonary embolism	0/1756	1/1737 (0.1)	—
Venous thromboembolism–related death	0/1756	0/1737	—
Asymptomatic proximal deep-vein thrombosis	1/1661 (0.1)	7/1637 (0.4)	—
Major venous thromboembolism‡	1/1661 (0.1)	13/1640 (0.8)	0.12 (0.02–0.84)

* The primary efficacy outcome of venous thromboembolism was a composite of symptomatic distal or proximal deep-vein thrombosis, pulmonary embolism, or venous thromboembolism–related death throughout the treatment period or asymptomatic proximal deep-vein thrombosis at the end of treatment. The risk ratios were estimated by multiple imputation, and marginal estimates are reported.
† Among the 13 patients with symptomatic deep-vein thromboses, 9 patients had an event on the day of compression ultrasonography at the end of immobilization (Table S5).
‡ Major venous thromboembolism was defined as pulmonary embolism or proximal deep-vein thrombosis.

SAFETY OUTCOMES

The frequency of bleeding events did not differ significantly between the rivaroxaban group and the enoxaparin group (1.1% and 1.0%, respectively, for major bleeding or nonmajor clinically relevant bleeding; risk ratio with multiple imputation, 1.04; 95% CI, 0.55 to 2.00). The incidence of major bleeding was 0.6% in the rivaroxaban group and 0.7% in the enoxaparin group (Table 3). In a post hoc analysis, the percentage of patients with the net clinical benefit outcome (a composite of efficacy and safety) was lower in the rivaroxaban group (0.8%) than in the enoxaparin group (1.8%), corresponding to a 52% lower incidence in the rivaroxaban group (Table 3).

DISCUSSION

In this trial of pharmacologic thromboprophylaxis after nonmajor orthopedic surgery, treatment with rivaroxaban, an orally active direct inhibitor of factor Xa, was associated with a 75% lower risk of major venous thromboembolism through the end of treatment than enoxaparin (0.2% vs. 1.1%). The use of rivaroxaban was not associated with a higher incidence of major bleeding or other bleeding events.

Current guidelines differ widely in their recommendations for thromboprophylaxis in nonmajor orthopedic surgery. The ninth American College of Chest Physicians guidelines,[2] published in 2012, suggest that prophylaxis is not needed in patients with isolated lower-leg injuries and leg immobilization, but the grade of recommendation is very weak (grade 2C). In contrast, other national or international guidelines encourage the use of prophylaxis with low-molecular-weight heparin during the period of immobilization in patients who have additional risk factors for venous thromboembolism, after a discussion between the treating physician and the patient about the potential benefits and harms.[4,7,8] In this context, the choice of enoxaparin rather than placebo as a comparator in our trial reflected the

Subgroup	Rivaroxaban	Enoxaparin	Risk Ratio (95% CI)
	no. of events/total no. of patients		
Intended treatment duration			
2 Wk to 1 mo	2/1016	3/993	0.75 (0.15–3.69)
>1 Mo to 2 mo	2/599	15/605	0.19 (0.05–0.72)
>2 Mo	0/46	0/42	—
Age			
<55 yr	3/1241	12/1242	0.30 (0.09–0.97)
≥55 yr	1/420	6/398	0.23 (0.04–1.39)
Body-mass index			
<30	3/1294	11/1285	0.34 (0.10–1.13)
≥30	1/367	7/355	0.21 (0.04–1.24)
History of trauma			
Yes	0/414	8/449	0.09 (0.01–1.39)
No	4/1239	10/1185	0.44 (0.15–1.32)
Type of surgery			
Ligament repair of the knee	2/607	4/586	0.58 (0.13–2.62)
Ankle arthrodesis, ankle fracture, or arthrodesis of leg articulation	1/353	3/327	0.43 (0.06–2.89)
Tibial transposition or patellar or tibial fracture	0/158	3/165	0.27 (0.02–3.48)
Tibial plateau or osteotomy	0/132	2/145	0.44 (0.04–4.80)
Ligament repair of ankle, Achilles' tendon repair, or hip arthroscopy	0/126	4/137	0.24 (0.01–3.87)
Foot surgery, knee arthroscopy, or removal of material	0/179	0/189	—
Unicompartmental knee prosthesis or femoral fracture	0/45	2/31	0.16 (0.01–3.26)
Other orthopedic surgery	1/61	0/60	4.69 (0.21–106.19)
Type of anesthesia			
General	3/607	10/636	0.37 (0.11–1.22)
Neuraxial	1/798	5/732	0.33 (0.06–1.93)
Peripheral-nerve block	0/156	2/159	0.44 (0.01–2.37)
Combined	0/100	1/113	0.37 (0.01–9.25)
Prophylactic LMWH before surgery			
Yes	3/234	6/233	0.51 (0.14–1.85)
No	1/1427	12/1407	0.16 (0.03–0.84)
LMWH after surgery			
Yes	0/142	3/131	0.18 (0.01–3.26)
No	4/1519	15/1509	0.31 (0.11–0.88)
Country			
Hungary	1/448	2/444	0.59 (0.09–3.94)
Czech Republic	3/221	5/229	0.64 (0.17–2.42)
France	0/214	6/211	0.12 (0.01–1.92)
Greece	0/169	2/168	0.40 (0.03–6.15)
Poland	0/174	1/163	0.32 (0.01–3.54)
Spain	0/137	1/139	0.14 (0.01–2.81)
Germany	0/40	1/38	0.54 (0.06–4.49)
Tunisia	0/152	0/141	—
Italy	0/104	0/104	—
Netherlands	0/2	0/3	—

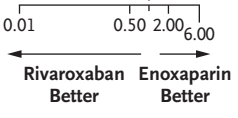


Figure 2. Treatment Effect across Prespecified Subgroups.

The subgroup analyses were conducted in the intention-to-treat population. Risk ratios and confidence intervals were determined with the use of multiple imputation for patients with missing data. The size of each square indicates the treatment effect, and arrows indicate 95% confidence intervals that extend past the boundary of the graph. The body-mass index is the weight in kilograms divided by the square of the height in meters. LMWH denotes low-molecular-weight heparin.

Table 3. Secondary Outcomes.*

Outcome	Rivaroxaban (N=1809)	Enoxaparin (N=1795)	Risk Ratio (95% CI)	P Value
	no. of patients with event/total no. of patients (%)			
Major bleeding or nonmajor clinically relevant bleeding	19/1757 (1.1)	18/1739 (1.0)	1.04 (0.55–2.00)	0.89
Major bleeding	10/1757 (0.6)	12/1739 (0.7)	0.81 (0.35–1.88)	0.62
Nonmajor clinically relevant bleeding	9/1757 (0.5)	6/1739 (0.3)	1.48 (0.52–4.17)	0.46
Overt thrombocytopenia	1/1756 (0.1)	0/1737	3.06 (0.13–70.85)	0.48
Death from any cause	0/1756	1/1737 (0.1)	0.63 (0.17–2.36)	0.49
Net clinical benefit†	14/1668 (0.8)	30/1643 (1.8)	0.48 (0.26–0.90)	—

* The analyses of secondary outcomes were for adjudicated events. Major bleeding was defined as fatal, critical, or clinically overt bleeding or bleeding at the surgical site leading to intervention.[11] Risk ratios were estimated with the use of multiple imputation, and marginal estimates are reported.

† Net clinical benefit was assessed in a post hoc analysis that compared the composite of venous thromboembolism or major bleeding between groups. Because this was a post hoc analysis, no statistical test was performed.

fact that low-molecular-weight heparin is routinely used for thromboprophylaxis in patients undergoing nonmajor orthopedic surgery in European hospitals.

The use of low-molecular-weight heparin in nonmajor orthopedic surgery is supported by two meta-analyses: one involving patients with reduced mobility undergoing nonmajor orthopedic surgery[3] and another involving patients undergoing foot and ankle surgery.[12] Both studies showed a significantly lower risk of venous thromboembolic events with low-molecular-weight heparin than with control.[3,12] However, these lower risks were driven primarily by a lower incidence of distal deep-vein thromboses. The relevance of such events, and whether they lead to further treatment, is a subject of debate.[13] In the open-label Prevention of Thrombosis after Knee Arthroscopy (POT-KAST) trial,[14] which focused on symptomatic events, low-molecular-weight heparin prophylaxis was compared with no prophylaxis in patients undergoing knee arthroscopy without immobilization. The study showed no meaningful between-group difference in the risk of symptomatic events (0.7% in the treatment group vs. 0.4% in the control group; relative risk, 1.6; 95% CI, 0.4 to 6.8), which suggests that low-molecular-weight heparin is ineffective in this population.

In our trial, the superiority of rivaroxaban was driven mainly by a significantly lower incidence of symptomatic events (relative risk, 0.28) (Table 2), which could reflect the inclusion of patients at higher risk than the patients involved in previous studies. Nevertheless, there is a need to better identify patients who are at high risk for an event and who would benefit most from thromboprophylaxis.

The limitations of our trial include the premature discontinuation of enrollment resulting in a smaller-than-planned sample size, which may limit the precision of the efficacy estimation. However, the results remained blinded at the time that the decision was made, and the observed treatment effect was more pronounced than expected (75% vs. 55% lower risk). The trial did not collect information on patients who did not meet the screening criteria, the population was relatively young and healthy, and the results may not be generalizable to older patients. The trial did not include a placebo group and therefore cannot provide information about event rates in a population that did not receive prophylaxis. The selection of patients for prophylaxis and the intended duration of prophylaxis were determined on the basis of physician judgment, which may be difficult to replicate in clinical practice. A notable percentage (8.4%) of the trial participants had an incomplete assessment or no assessment of the primary outcome. Not all the events that occurred during the 30 days (within a window of ±7 days)

after the discontinuation of anticoagulation were confirmed by objective tests and submitted to the clinical-events committee. Finally, the small numbers of events mean that the trial had very limited power to evaluate subgroup effects.

This trial showed that treatment with oral rivaroxaban was superior to subcutaneous enoxaparin with regard to the prevention of venous thromboembolism in patients undergoing nonmajor orthopedic surgery with a period of immobilization. There was no significant difference between rivaroxaban and enoxaparin in the risk of major bleeding events.

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APPENDIX

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