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Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

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ABSTRACT

BACKGROUND

Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) after total hip or total knee arthroplasty, but comparisons with direct oral anticoagulants are lacking for prophylaxis beyond hospital discharge.

METHODS

We performed a multicenter, double-blind, randomized, controlled trial involving patients who were undergoing total hip or knee arthroplasty. All the patients received once-daily oral rivaroxaban (10 mg) until postoperative day 5 and then were randomly assigned to continue rivaroxaban or switch to aspirin (81 mg daily) for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty. Patients were followed for 90 days for symptomatic venous thromboembolism (the primary effectiveness outcome) and bleeding complications, including major or clinically relevant nonmajor bleeding (the primary safety outcome).

RESULTS

A total of 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoing total knee arthroplasty) were enrolled in the trial. Venous thromboembolism occurred in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI], −0.55 to 0.66; P<0.001 for noninferiority and P=0.84 for superiority). Major bleeding complications occurred in 8 patients (0.47%) in the aspirin group and in 5 (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, −0.65 to 0.29; P=0.42). Clinically important bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI, −1.07 to 0.47; P=0.43).

CONCLUSIONS

Among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT01720108.)

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Deep-vein thrombosis and pulmonary embolism (collectively known as venous thromboembolism) are well-recognized complications after total hip or total knee arthroplasty.[1,2] The perioperative administration of anticoagulant prophylaxis has proved to reduce the rates of death and complications associated with venous thromboembolism after these procedures. Additional benefit is observed by extending prophylaxis beyond hospital discharge, particularly after total hip arthroplasty.[3-5] Evidence-based guidelines recommend that patients who are undergoing total hip or total knee arthroplasty receive anticoagulant prophylaxis for a minimum of 14 days and suggest that such prophylaxis continue for up to 35 days after surgery.[6] The direct oral anticoagulants are commonly prescribed for extended prophylaxis because of their effectiveness, safety, and convenience of use.[7-11]

Aspirin is an inexpensive, generic, and widely available antiplatelet drug. Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism postoperatively, but comparisons with direct oral anticoagulants are lacking.[12-14] We reasoned that aspirin, because of its efficacy, low cost, and well-established side-effect profile, was potentially a good choice for extended prophylaxis after total hip or total knee arthroplasty. In the EPCAT II (Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty II) trial, we studied the effectiveness and safety of extended prophylaxis with aspirin as compared with the direct oral anticoagulant rivaroxaban for the prevention of venous thromboembolism after total hip or total knee arthroplasty among patients who had received a short postoperative course of rivaroxaban prophylaxis.

Methods

Patients and Trial Oversight

We conducted this double-blind, randomized, controlled trial at 15 university-affiliated health centers in Canada. All the patients who were undergoing elective unilateral primary or revision hip or knee arthroplasty were potentially eligible for the trial. Key exclusion criteria were hip or lower limb fracture during the previous 3 months and metastatic cancer. (A complete list of the exclusion criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) A history of long-term use of aspirin at a dose of less than 100 mg per day was permitted, and the perioperative administration of such aspirin was done at the discretion of the attending physician.

The trial was approved by the research ethics board at each trial center and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All the patients provided written informed consent. The trial was designed by the authors and supported by the Canadian Institutes of Health Research, which was not involved in the trial design, conduct, or analyses. There was no industry support or funding. The trial was monitored by an independent data and safety monitoring board. The results were collected and analyzed by the authors, who vouch for the data, its analysis, and adherence to the protocol, available at NEJM.org. No interim analysis was planned in the protocol or performed on the basis of the recommendation of the data and safety monitoring board. No one who is not an author contributed to the writing of the manuscript.

Trial Procedures and Randomization

Technical aspects of the total hip or total knee arthroplasty procedures were left to the clinical discretion of the attending surgeons. All the patients received in-hospital prophylaxis with oral rivaroxaban (Xarelto, Bayer Pharma) at a dose of 10 mg once daily, starting on the day of the surgery (not less than 6 hours after wound closure) or on postoperative day 1, depending on local practice; this regimen was followed by daily administration up to and including postoperative day 5. Patients who were undergoing total knee arthroplasty were then randomly assigned to receive an additional 9 days of thromboprophylaxis with either 10 mg of oral rivaroxaban or 81 mg of aspirin (Bayer Pharma) once daily, starting on postoperative day 6. Patients who were undergoing total hip arthroplasty were randomly assigned to receive an additional 30 days of once-daily rivaroxaban (10 mg) or aspirin (81 mg), starting on postoperative day 6. Rivaroxaban and aspirin were administered in identical-appearing opaque gelatin capsules. Patients who had been taking daily low-dose aspirin before randomization (long-term aspirin subgroup) took

open-label aspirin at a dose of less than 100 mg per day, as prescribed by their physician, in addition to the assigned trial regimen.

Trial-group assignments were performed between postoperative day 2 and day 6 with the use of randomly generated numbers permuted in blocks of four or six. Randomization was stratified according to surgical procedure, trial center, and use or nonuse of long-term aspirin therapy.

TRIAL OUTCOMES

The primary effectiveness outcome was adjudicated symptomatic venous thromboembolism, which was defined as deep-vein thrombosis involving the popliteal vein or more proximal leg veins (including the femoral, common femoral, and iliac veins and inferior vena cava) or pulmonary embolism, as confirmed by objective testing in the 90-day period after randomization. The primary safety outcome was bleeding, including major or clinically relevant nonmajor bleeding. (Details are provided in the Supplementary Appendix.)

Secondary outcome measures were death, myocardial infarction, stroke, and wound infection. No screening tests for deep-vein thrombosis or pulmonary embolism were performed in asymptomatic patients. We used standardized algorithms to evaluate patients in whom symptoms of deep-vein thrombosis or pulmonary embolism had developed, as described in the trial protocol. Patients with suspected deep-vein thrombosis underwent compression ultrasonography from the common femoral vein to at least the trifurcation of the popliteal vein, and the diagnosis of deep-vein thrombosis was made on the basis of previously validated criteria.[15] Patients with symptoms of pulmonary embolism were evaluated with ventilation–perfusion lung scanning or computed tomographic pulmonary angiography, and a diagnosis was made on the basis of previously validated criteria.[16] Patients in whom deep-vein thrombosis or pulmonary embolism was suspected and excluded by objective testing continued to receive the trial medication, did not receive additional anticoagulant therapy, and were followed over the 90-day period after randomization.

The primary safety end point was adjudicated bleeding, which was defined as major or clinically relevant nonmajor bleeding on the basis of previously described criteria (see the Supplementary Appendix).[12] An independent adjudication committee whose members were unaware of trial-group assignments determined the final categorization after a review of the laboratory, radiographic, and clinical assessments performed in all the patients with suspected outcome events.

STATISTICAL ANALYSIS

The estimated baseline rate of venous thromboembolism in the rivaroxaban group was 1.0%. A minimal clinically important difference was established to be 1.0 percentage point on the basis of a survey of Canadian thromboembolism experts and orthopedic surgeons. Using a noninferiority design, we calculated that a sample size of 1696 patients per group would provide a power of 90% to show that aspirin was noninferior to rivaroxaban for the prevention of the primary effectiveness outcome. To account for withdrawal of consent or loss to follow-up over the course of the trial, we increased the final sample size by 1%, to 3426. Noninferiority was analyzed only for the primary effectiveness outcome.

The primary analysis was performed on the intention-to-treat principle. We compared overall event rates using a noninferiority analysis for the risk difference on the basis of the Wald method. We used Fisher's exact test to determine whether the two groups differed. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

From January 2013 through April 2016, a total of 3753 patients who had met the eligibility criteria consented to participate (Fig. 1). Of these patients, 98 withdrew their consent before randomization, and an additional 228 patients were excluded during the postoperative period before randomization. The remaining 3427 patients underwent randomization. Three patients withdrew consent after randomization and were not included in any of the analyses. One patient in the rivaroxaban group did not complete the follow-up assessments but was known to be alive at 90 days. No other patients were lost to follow-up.

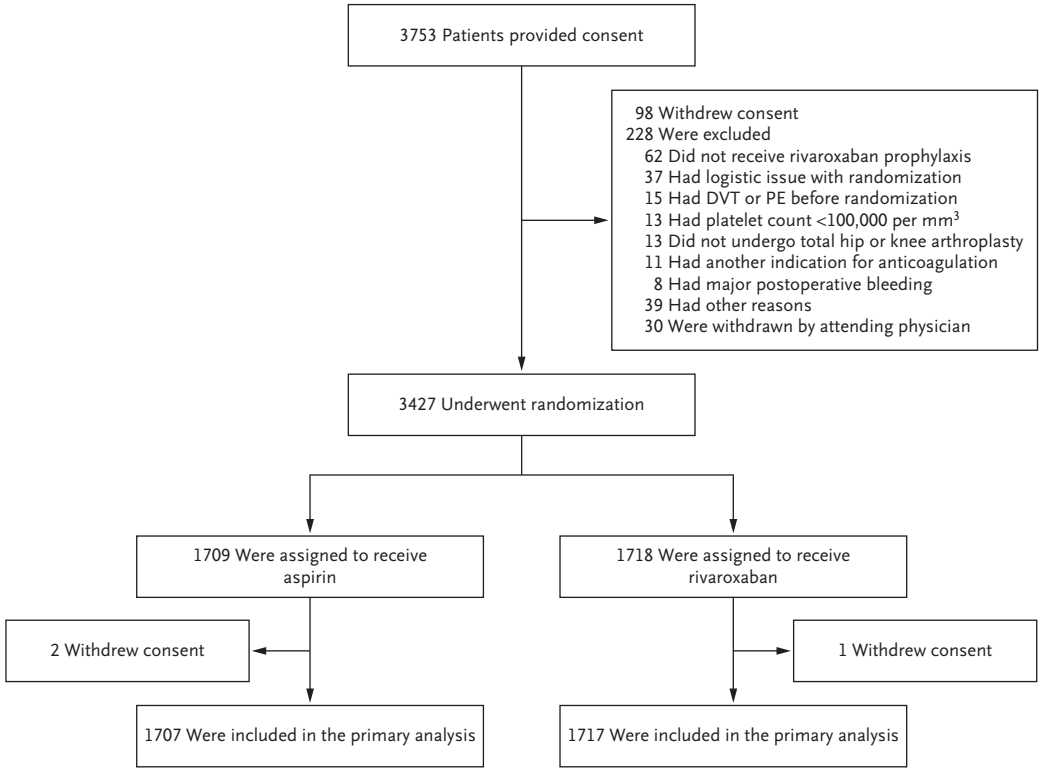

Figure 1. Enrollment and Outcomes.
DVT denotes deep-vein thrombosis, and PE pulmonary embolism.

The demographic, medical, and surgical characteristics of the patients in the two groups were similar (Table 1). A total of 1804 patients underwent total hip arthroplasty, and 1620 underwent total knee arthroplasty. The mean age of the patients was 62.8 years, and 47.8% were men. More than 90% of the patients underwent primary arthroplasty procedures, and the average length of the hospital stay after surgery was 3.5 days in the two groups. At the time of randomization, long-term aspirin prophylaxis was being administered in 855 patients: 372 patients (20.6%) who were undergoing total hip arthroplasty and 483 (29.8%) who were undergoing total knee arthroplasty.

PRIMARY OUTCOMES

During the 90-day follow-up period, symptomatic proximal deep-vein thrombosis or pulmonary embolism developed in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI], −0.55 to 0.66) (Table 2). In the comparison with rivaroxaban, aspirin was found to be noninferior ($P<0.001$) but not superior ($P=0.84$) for the prevention of postoperative proximal deep-vein thrombosis or pulmonary embolism.

One death from pulmonary embolism occurred in the aspirin group in a patient who had undergone total knee arthroplasty. The death occurred 31 days after randomization and 17 days after the completion of aspirin prophylaxis. There were no other deaths during the trial.

Major bleeding events occurred in 8 patients (0.47%) in the aspirin group and in 5 patients (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, −0.65 to 0.29; $P=0.42$) (Table 2). A combination of major bleeding and clinically relevant nonmajor bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI,

Table 1. Characteristics of the Patients at Baseline, According to Surgical Subgroup.*

Characteristic	Total Hip Arthroplasty		Total Knee Arthroplasty		All Patients	
	Rivaroxaban (N=902)	Aspirin (N=902)	Rivaroxaban (N=815)	Aspirin (N=805)	Rivaroxaban (N=1717)	Aspirin (N=1707)
Age — yr	60.9±11.0	61.3±11.1	64.7±8.4	64.6±8.7	62.7±10.1	62.9±10.1
Male sex — no. (%)	480 (53.2)	486 (53.9)	353 (43.3)	318 (39.5)	833 (48.5)	804 (47.1)
Body-mass index†	29.4±5.8	29.4±6.0	32.7±6.8	33.0±7.2	31.0±6.6	31.1±6.8
Risk factors — no. (%)						
Previous venous thromboembolism	22 (2.4)	20 (2.2)	22 (2.7)	17 (2.1)	44 (2.6)	37 (2.2)
Previous surgery	28 (3.1)	30 (3.3)	18 (2.2)	28 (3.5)	46 (2.7)	58 (3.4)
Cancer	19 (2.1)	17 (1.9)	19 (2.3)	25 (3.1)	38 (2.2)	42 (2.5)
Current smoker	86 (9.5)	83 (9.2)	71 (8.7)	79 (9.8)	157 (9.1)	162 (9.5)
Hemoglobin — g/liter	140.4±12.5	140.2±13.0	138.2±12.8	138.0±12.8	139.4±12.7	139.2±12.9
Mean platelet count per mm^3	241,200	238,700	240,700	244,100	240,900	241,200
Type of surgery — no. (%)						
Primary	802 (88.9)	809 (89.7)	770 (94.5)	760 (94.4)	1572 (91.6)	1569 (91.9)
Revision	64 (7.1)	52 (5.8)	44 (5.4)	42 (5.2)	108 (6.3)	94 (5.5)
Resurfacing	35 (3.9)	41 (4.5)	NA	NA	35 (2.0)	41 (2.4)
Other	1 (0.1)	0	1 (0.1)	3 (0.4)	2 (0.1)	3 (0.2)
Use of tranexamic acid — no./total no. (%)	478/898 (53.2)	470/901 (52.2)	456/812 (56.2)	455/802 (56.7)	934/1710 (54.6)	925/1703 (54.3)
Postoperative mechanical compression — no./total no. (%)						
Pneumatic compression	93/155 (60.0)	94/162 (58.0)	50/119 (42.0)	44/114 (38.6)	143/274 (52.2)	138/276 (50.0)
Graduated stockings	45/155 (29.0)	53/162 (32.7)	62/119 (52.1)	65/114 (57.0)	107/274 (39.1)	118/276 (42.8)
Both	17/155 (11.0)	15/162 (9.3)	7/119 (5.9)	5/114 (4.4)	24/274 (8.8)	20/276 (7.2)
Anesthetic — no. (%)						
General	263 (29.2)	288 (31.9)	214 (26.3)	205 (25.5)	477 (27.8)	493 (28.9)
Regional	628 (69.6)	605 (67.1)	597 (73.3)	596 (74.0)	1225 (71.3)	1201 (70.4)
Both	11 (1.2)	9 (1.0)	4 (0.5)	4 (0.5)	15 (0.9)	13 (0.8)
Time in operating room — hr	1.4±0.6	1.4±0.6	1.4±0.5	1.4±0.5	1.4±0.6	1.4±0.6
Estimated blood loss — ml	369±270	374±295	227±174	234±172	307±244	314±259
Length of hospital stay — days	3.3±1.6	3.4±1.9	3.6±1.6	3.6±1.5	3.4±1.6	3.5±1.8
Surgical approach — no. (%)						
Direct lateral	425 (47.1)	421 (46.7)	NA	NA	425 (24.8)	421 (24.7)
Posterior	386 (42.8)	391 (43.3)	NA	NA	386 (22.5)	391 (22.9)
Anterolateral	49 (5.4)	50 (5.5)	NA	NA	49 (2.9)	50 (2.9)
Anterior	42 (4.7)	40 (4.4)	NA	NA	42 (2.4)	40 (2.3)
Anterior longitudinal midline	NA	NA	815 (100)	805 (100)	815 (47.5)	805 (47.2)
Prosthesis — no. (%)						
Cemented	57 (6.3)	49 (5.4)	742 (91.0)	727 (90.3)	799 (46.5)	776 (45.5)
Hybrid	56 (6.2)	55 (6.1)	47 (5.8)	55 (6.8)	103 (6.0)	110 (6.4)
Noncemented	789 (87.5)	798 (88.5)	25 (3.1)	23 (2.9)	814 (47.4)	821 (48.1)
Missing data	0	0	1 (0.1)	0	1 (0.1)	0

* Plus–minus values are means ±SD. None of the between-group comparisons were significant at baseline. NA denotes not applicable.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Primary Effectiveness and Safety Outcomes.

Outcome	Rivaroxaban (N=1717)	Aspirin (N=1707)	P Value
	no. of patients (%)		
Venous thromboembolism	12 (0.70)	11 (0.64)	0.84*
Pulmonary embolism	6 (0.35)	5 (0.29)	
Proximal deep-vein thrombosis	4 (0.23)	4 (0.23)	
Pulmonary embolism and proximal deep-vein thrombosis	2 (0.12)	2 (0.12)	
Major bleeding	5 (0.29)	8 (0.47)	0.42
Any bleeding†	17 (0.99)	22 (1.29)	0.43

* P<0.001 for noninferiority, as defined by the upper boundary of the 95% confidence interval for the absolute between-group difference.
† This category includes major bleeding and clinically relevant nonmajor bleeding.

–1.07 to 0.47; P=0.43). All bleeding events consisted of overt hemorrhage at the surgical site. Most bleeding events took place within 10 days after randomization.

SUBGROUP ANALYSES

There were no significant between-group differences in rates of thromboembolic events or major or clinically relevant nonmajor bleeding complications in the total hip or total knee arthroplasty subgroups (Table 3). Similar rates of thromboembolism, major bleeding, and clinically relevant nonmajor bleeding occurred among the 855 patients who were receiving long-term aspirin therapy and in the 2569 patients who were not receiving such therapy (Table 4).

DEEP-VEIN THROMBOSIS IN THE CALF

Symptomatic deep-vein thrombosis that was isolated to the calf veins (which was not analyzed as a primary outcome of the trial) occurred in 8 patients in the aspirin group and in 5 patients in the rivaroxaban group. One episode of such thrombosis occurred after total hip arthroplasty in a patient in the aspirin group, and the remainder of the events occurred after total knee arthroplasty.

DISCUSSION

In our trial, we found that the inexpensive, widely available generic agent aspirin was not significantly different from the more expensive, direct

Table 3. Primary Effectiveness and Safety Outcomes, According to Surgical Procedure.

Outcome	Total Hip Arthroplasty			Total Knee Arthroplasty		
	Rivaroxaban (N=902)	Aspirin (N=902)	P Value	Rivaroxaban (N=815)	Aspirin (N=805)	P Value
	no. (%)			*no. (%)*		
Venous thromboembolism	5 (0.55)	4 (0.44)	1.00*	7 (0.86)	7 (0.87)	1.00†
Pulmonary embolism	2 (0.22)	2 (0.22)		4 (0.49)	3 (0.37)	
Proximal deep-vein thrombosis	1 (0.11)	1 (0.11)		3 (0.37)	3 (0.37)	
Pulmonary embolism and proximal deep-vein thrombosis	2 (0.22)	1 (0.11)		0	1 (0.12)	
Major bleeding	3 (0.33)	3 (0.33)	1.00	2 (0.25)	5 (0.62)	0.29
All bleeding‡	7 (0.78)	11 (1.22)	0.48	10 (1.23)	11 (1.37)	0.83

* P=0.001 for noninferiority.
† P=0.03 for noninferiority.
‡ This category includes major bleeding and clinically relevant nonmajor bleeding.

Table 4. Subgroup Analysis of Primary Outcomes, According to Use of Long-Term Aspirin Therapy.

Outcome	Long-Term Aspirin Therapy			No Long-Term Aspirin Therapy		
	Rivaroxaban (N=429)	Aspirin (N=426)	P Value	Rivaroxaban (N=1288)	Aspirin (N=1281)	P Value
	no. (%)			*no. (%)*		
Venous thromboembolism	3 (0.70)	3 (0.70)	1.00	9 (0.70)	8 (0.62)	1.00*
Major bleeding	1 (0.23)	4 (0.94)	0.22	4 (0.31)	4 (0.31)	1.00
All bleeding†	5 (1.17)	8 (1.88)	0.42	12 (0.93)	14 (1.09)	0.70

* P<0.001 for noninferiority.
† This category includes major and clinically relevant nonmajor bleeding.

oral anticoagulant rivaroxaban for the prevention of symptomatic, clinically important venous thromboembolism after total hip or total knee arthroplasty among patients who had received an initial 5-day postoperative course of rivaroxaban. The patients in the two trial groups had low and very similar rates of symptomatic thromboembolic complications during the 90-day follow-up period after randomization (0.64% with aspirin and 0.70% with rivaroxaban, for a difference of 0.06 percentage points [95% CI, −0.55 to 0.66]). Furthermore, the upper boundary of the 95% confidence interval for the absolute difference between groups was well under 1%, which met our criterion for noninferiority. Rates of clinically important bleeding complications were less than 1.5% and did not differ significantly between the two groups. All the bleeding events occurred at the surgical site.

Aspirin and rivaroxaban were similarly effective for preventing venous thromboembolism after either total hip or total knee arthroplasty. There were no between-group differences in effectiveness in the subgroup of patients who were receiving long-term aspirin therapy, which suggests that there was no benefit of adding 81 mg of aspirin to either aspirin or rivaroxaban prophylaxis. However, there were suggestions of more major and clinically relevant nonmajor bleeding among patients in the long-term aspirin subgroup, particularly among those who had been assigned to the aspirin group and hence were receiving a second daily dose of aspirin prophylaxis.

Our results are aligned with and extend the results of the EPCAT I (Extended Prophylaxis Comparing Low-Molecular-Weight Heparin to Aspirin in Total Hip Arthroplasty I) trial, which suggested that extended prophylaxis with aspirin for 28 days after total hip arthroplasty was as safe and effective as low-molecular-weight heparin to prevent venous thromboembolism after an initial 10-day postoperative course of low-molecular-weight heparin.[12] The EPCAT II trial provides additional information to support the use of aspirin for the secondary prevention of venous thromboembolism after joint arthroplasty. Although there have been few recent randomized, controlled trials of aspirin for prophylaxis after joint arthroplasty, several cohort and registry studies have suggested that aspirin prophylaxis was associated with low rates of thromboembolic complications after total hip or total knee arthroplasty, similar to the rates with oral anticoagulant therapy.[17-20]

Our trial has several limitations. Since the recruitment of patients frequently occurred postoperatively, the trial population did not consist of an entire inception cohort treated in accordance with a standardized protocol. Thus, we could not calculate the absolute event rates of thromboembolic or bleeding complications associated with each of the two prophylaxis strategies. However, our findings provide clear evidence for the relative effectiveness and safety of extended prophylaxis with aspirin and rivaroxaban after an initial 5-day postoperative course of rivaroxaban.

Similarly, since most bleeding events that were related to surgical-site bleeding occurred early after randomization, it is difficult to determine whether bleeding was predominantly related to the initial postoperative rivaroxaban, to the trial medication, or to a combination of the two.

This factor could potentially result in an overestimation of the rate of aspirin-related bleeding. A true comparison of the overall rates of bleeding associated with aspirin versus rivaroxaban after joint arthroplasty would require a head-to-head randomized, controlled trial of the two medications, with both therapies started during the immediate postoperative period.

Finally, for logistical reasons, patients often underwent randomization at the time of hospital discharge before postoperative day 5. Because of this timing, some of the trial events occurred before postoperative day 6, when the trial medication was started. According to the intention-to-treat analysis, these events were included in the primary analysis.

Despite these limitations, our findings are clinically important. The trial was large and adequately powered to show the noninferiority of aspirin as compared with rivaroxaban. We chose clinically relevant and important end points for the primary effectiveness analysis. Only symptomatic proximal deep-vein thrombosis and pulmonary embolism for which patients sought medical attention and had the events confirmed by objective testing were counted as outcome events. All the patients were followed for 90 days to ensure that no clinically important events were missed, and no patients were lost to follow-up. The conduct of the trial and review by an independent adjudication committee were performed in a blinded manner, and an independent data and safety monitoring board oversaw the execution of the trial.

In conclusion, we found that aspirin was not significantly different from the direct oral anticoagulant rivaroxaban for the prevention of clinically important, symptomatic events of proximal deep-vein thrombosis or pulmonary embolism after total hip or total knee arthroplasty after an initial 5-day postoperative course of rivaroxaban.

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

APPENDIX

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