ORIGINAL ARTICLE

Prevention of Venous Thromboembolism after Total Hip or Knee Replacement

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ABSTRACT

BACKGROUND

Studies comparing aspirin with anticoagulants for venous thromboembolism (VTE) prophylaxis after total hip or knee arthroplasty have had conflicting results.

METHODS

In a comparative-effectiveness noninferiority trial, we randomly assigned patients undergoing elective hip or knee arthroplasty to receive aspirin (81 mg twice daily), warfarin (to a target international normalized ratio of 2.0), or rivaroxaban (10 mg daily) for 30 days. The composite primary effectiveness outcome (death from any cause or symptomatic VTE) and primary safety outcome (bleeding, reoperation for wound problems, or myocardial infarction) were evaluated through 6 months in a blinded fashion. The noninferiority margin for the risk difference was 0.69 percentage points.

RESULTS

Among 18,883 participants who had undergone randomization, 15,317 (7214 with hip arthroplasty and 8103 with knee arthroplasty) were included in the primary per-protocol analysis. A primary effectiveness outcome event occurred in 77 of 6090 participants (1.26%) in the aspirin group, in 52 of 4231 (1.23%) in the warfarin group, and in 47 of 4996 (0.94%) in the rivaroxaban group; a primary safety outcome event occurred in 177 (2.91%), 142 (3.36%), and 174 (3.48%), respectively. In pairwise comparisons, 6-month risks of a primary effectiveness outcome event were 1.24% and 0.94% for aspirin versus rivaroxaban (difference, 0.30 percentage points; 95% confidence interval [CI], −0.20 to 0.81); 1.24% and 1.01% for aspirin versus warfarin (difference, 0.23 percentage points; 95% CI, −0.34 to 0.81); and 1.13% and 1.10% for warfarin versus rivaroxaban (difference, 0.03 percentage points; 95% CI, −0.57 to 0.63). Risks of a primary safety outcome event were 3.70% and 3.02% for rivaroxaban versus aspirin (difference, 0.68 percentage points; 95% CI, −0.04 to 1.41); 3.65% and 2.88% for warfarin versus aspirin (difference, 0.77 percentage points; 95% CI, −0.04 to 1.58); and 3.59% and 3.61% for rivaroxaban versus warfarin (difference, −0.02 percentage points; 95% CI, −0.89 to 0.85). Intention-to-treat analyses yielded similar results.

CONCLUSIONS

Aspirin prophylaxis after total hip or knee arthroplasty was not noninferior to rivaroxaban or warfarin with respect to death or symptomatic VTE. Warfarin and rivaroxaban were not noninferior to aspirin for safety. (Funded by the Patient-Centered Outcomes Research Institute; PEPPER ClinicalTrials.gov number, NCT02810704.)

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*The PEPPER trial investigators and steering committee members are listed in the Supplementary Appendix, available at NEJM.org.

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Venous thromboembolism (VTE), including pulmonary embolism and deep-vein thrombosis (DVT), is potentially life-threatening after total hip or knee arthroplasty.[1,2] Evidence-based practice guidelines recommend pharmacologic prophylaxis, which can increase risks of serious bleeding and wound complications.[3-5] Effective strategies for balancing the risks of thromboembolism and bleeding remain elusive owing to conflicting observational study results and the large participant numbers needed for definitive trials.[6-9]

Aspirin is widely favored among orthopedic surgeons in the United States and Canada because of low cost, minimal bleeding risk, and the absence of required monitoring,[10,11] in addition to concerns about anticoagulants with regard to increased risks of bleeding and associated wound complications, readmission, or reoperation.[12-14] However, evidence to confirm the effectiveness of aspirin as compared with anticoagulants is scant.[15-20] Accordingly, we designed a large, multicenter trial powered to concurrently evaluate whether aspirin would be noninferior to both rivaroxaban and warfarin for effectiveness of VTE prophylaxis and whether rivaroxaban and warfarin would be noninferior to aspirin with respect to minimizing bleeding risk.

Methods

Trial Design

We conducted the Pulmonary Embolism Prevention after Hip and Knee Replacement (PEPPER) trial, a prospective, randomized, comparative-effectiveness trial, at 34 medical centers in the United States and Canada (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[21,22] The institutional review board at the Medical University of South Carolina served as a single institutional review board and oversaw 30 centers; the other 4 centers followed guidance from a local institutional review board. All the participants provided written informed consent, which may have been obtained electronically. The first, second, and third authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Trial Population and Conduct

All patients 21 years of age or older who were undergoing elective total hip or knee arthroplasty for osteoarthritis at the clinical centers were screened. Patients receiving long-term anticoagulation therapy were excluded. Preoperatively, participants were randomly assigned to one of the treatments that they were eligible to receive; patients were included only in analyses for which they were eligible to receive either of the treatments being compared. Randomization was conducted with the use of permuted blocks with stratification according to clinical center and procedure (hip or knee arthroplasty) and with the use of an independent online platform that concealed treatment sequences until assigned. Assignment was accessed by trial coordinators only after assessing eligibility and obtaining informed consent. Participants were assigned to receive chemoprophylaxis with aspirin, warfarin, or rivaroxaban for 30 days. For aspirin, treatment started with an initial dose of 162 mg in the holding area immediately before the operation, followed by 81 mg orally twice daily starting the day after surgery; for warfarin, treatment was initiated in the holding area before the operation and given each evening thereafter to achieve a target international normalized ratio of 2.0 (targeted range, 1.7 to 2.2); and for rivaroxaban, treatment was a fixed dose of 10 mg orally once daily, with initiation delayed until 24 hours after the completion of surgery to mitigate bleeding risk.

Despite a possibly greater bleeding risk with rivaroxaban than with apixaban, rivaroxaban was selected as a comparator owing to extensive study of its effects after arthroplasty.[23] It was deemed unethical to randomly assign participants considered to be at highest risk for life-threatening VTE to receive aspirin, specifically those with a history of pulmonary embolism or DVT within 6 months before the planned surgery or an active cancer diagnosis. No other determinants of high risk, such as obesity, diabetes, smoking, or peripheral vascular disease, precluded randomization to the aspirin group. Contraindications or adverse reactions to any trial drug precluded randomization to that drug. Eligibility for at least two of the trial regimens was required for trial participation.

At three clinical sites in the United States where high costs of rivaroxaban were unsupported by the 340B Drug Pricing Program, randomization was restricted to aspirin or warfarin; at five clinical sites that lacked warfarin-monitoring infrastructure, randomization was restricted to aspirin or rivaroxaban. Randomization to



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warfarin was discontinued in May 2023 owing to increasing crossovers (in 36.9% of the participants in the warfarin group) related to monitoring challenges after the coronavirus disease 2019 (Covid-19) pandemic; at that time, 15,845 participants had been enrolled (5132 to receive aspirin, 5389 to warfarin, and 5324 to rivaroxaban). Participants taking low-dose cardioprotective aspirin were advised to continue that medication. Pneumatic compression devices, surgical approach, implant selection, and anesthesia were used in accordance with local practice.

When the Covid-19 pandemic was declared in March 2020, a total of 10,457 (55%) patients had been enrolled. A pause in elective surgery prolonged enrollment from 3.5 years to 8 years.

OUTCOMES

The primary effectiveness outcome was a composite of death from any cause or symptomatic VTE as confirmed by objective testing and resulting in readmission or therapeutic anticoagulation. In our initial protocol, readmission was required for the diagnosis of VTE, but this requirement was changed before any data analyses occurred given that outpatient care became commonplace.[21] The primary safety outcome was a composite of bleeding (major, according to International Society on Thrombosis and Haemostasis criteria[24]; nonmajor wound-related; and upper gastrointestinal), reoperation for wound complications, removal of an infected implant, or myocardial infarction. Postoperative wound drainage (bloody or serosanguinous) beyond 5 days and delayed healing that led to care after 2 weeks were both surrogates for important nonmajor wound-related bleeding representing precursors to deep infection. Nonmajor non–wound-related bleeding was a secondary safety outcome.

Adverse events were adjudicated by an independent physician panel whose members were unaware of treatment assignments. Surveys at 1, 3, and 6 months, which were completed by participants online or in telephone interviews with interviewers who were unaware of treatment assignments or were sent by postage-paid reply mail, addressed unplanned medical visits and hospitalizations. These surveys were supplemented by local medical record review and ad hoc event reporting.[25] Participants without a 6-month survey were contacted by the enrolling center or underwent medical record review for adverse events or evidence of life, including a National Death Index query.

STATISTICAL ANALYSIS

Given the noninferiority design, our analysis used a modified per-protocol approach,[26-28] for which the primary estimand of analysis included only participants receiving the randomized treatment in the hospital and a prescription for the assigned trial drug at discharge.[29] Participants who were discharged with a different treatment were included in the analysis but had their data censored at discharge, and those who withdrew before 6 months had their data censored at withdrawal. The 6-month risk of a primary-outcome event (effectiveness or safety) was estimated with the use of a weighted Kaplan–Meier approach to balance the groups with respect to age, sex, clinical center, surgery date, educational level, employment status, and key coexisting conditions (i.e., those listed in the Charlson Comorbidity Index).[30]

Pairwise treatment comparisons included only those participants eligible for both treatments. The strict prespecified noninferiority margin of 0.69 percentage points was one third the projected 2% incidence of a primary effectiveness outcome event (and slightly more than half the aggregate incidence that we observed during the trial). For the effectiveness analyses, aspirin was hypothesized to be noninferior to warfarin or rivaroxaban with respect to effectiveness in the prevention of death or symptomatic VTE, and warfarin was hypothesized to be noninferior to rivaroxaban. For the safety analyses, warfarin and rivaroxaban were each hypothesized to be noninferior to aspirin with respect to avoidance of bleeding complications, and rivaroxaban was hypothesized to be noninferior to warfarin.

P values and the widths of the 95% confidence interval for the three noninferiority comparisons for the primary effectiveness outcome were adjusted for multiple comparisons with the use of a Bonferroni approach. No adjustment was made for multiple comparisons in secondary and subgroup analyses; associated 95% confidence intervals should not be used in place of hypothesis

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testing. Risk differences (with 95% confidence intervals) are reported for secondary and subgroup analyses. We prespecified subgroup analyses according to surgical site (hip or knee) given differences in pathophysiological characteristics of thrombogenesis and reported effects of prophylaxis.[19,31] Intention-to-treat and as-treated analyses were also conducted. The intention-to-treat analysis included all the participants according to their randomized group assignment, and the as-treated analysis included participants according to the treatment they received.

On the basis of published risks of death (0.1 to 0.3%), clinical VTE (1 to 2%), and bleeding (1% with aspirin, 1 to 2% with warfarin, and 3 to 5% with rivaroxaban) after total hip or knee arthroplasty,[5,12-19] we projected that, in both the primary composite effectiveness and safety analyses, 2% of the participants would have an outcome event. We calculated that the randomization of 24,444 participants, with an assumption that 10% would withdraw, would provide the trial with 85% power to reject inferiority. We revised the sample size downward in June 2020 because the observed overall percentage of participants with a primary effectiveness outcome event (1.1%) was lower than expected and the observed mortality (0.25%) was higher than expected, and we revised it again in May 2023, concurrent with the decision to discontinue randomization to warfarin when outpatient monitoring challenges increased warfarin crossovers after the Covid-19 pandemic. On the basis of data regarding group-specific treatment crossover, we calculated that the enrollment of 19,000 participants with an actual withdrawal of only 2.5% would provide 15,145 participants (with 6050 in the aspirin group, 4789 in the warfarin group, and 4306 in the rivaroxaban group) who could be evaluated and provide the trial with 80% power to rule out a risk difference of more than 0.69 percentage points for the primary effectiveness or safety outcome.

RESULTS

PARTICIPANT POPULATION

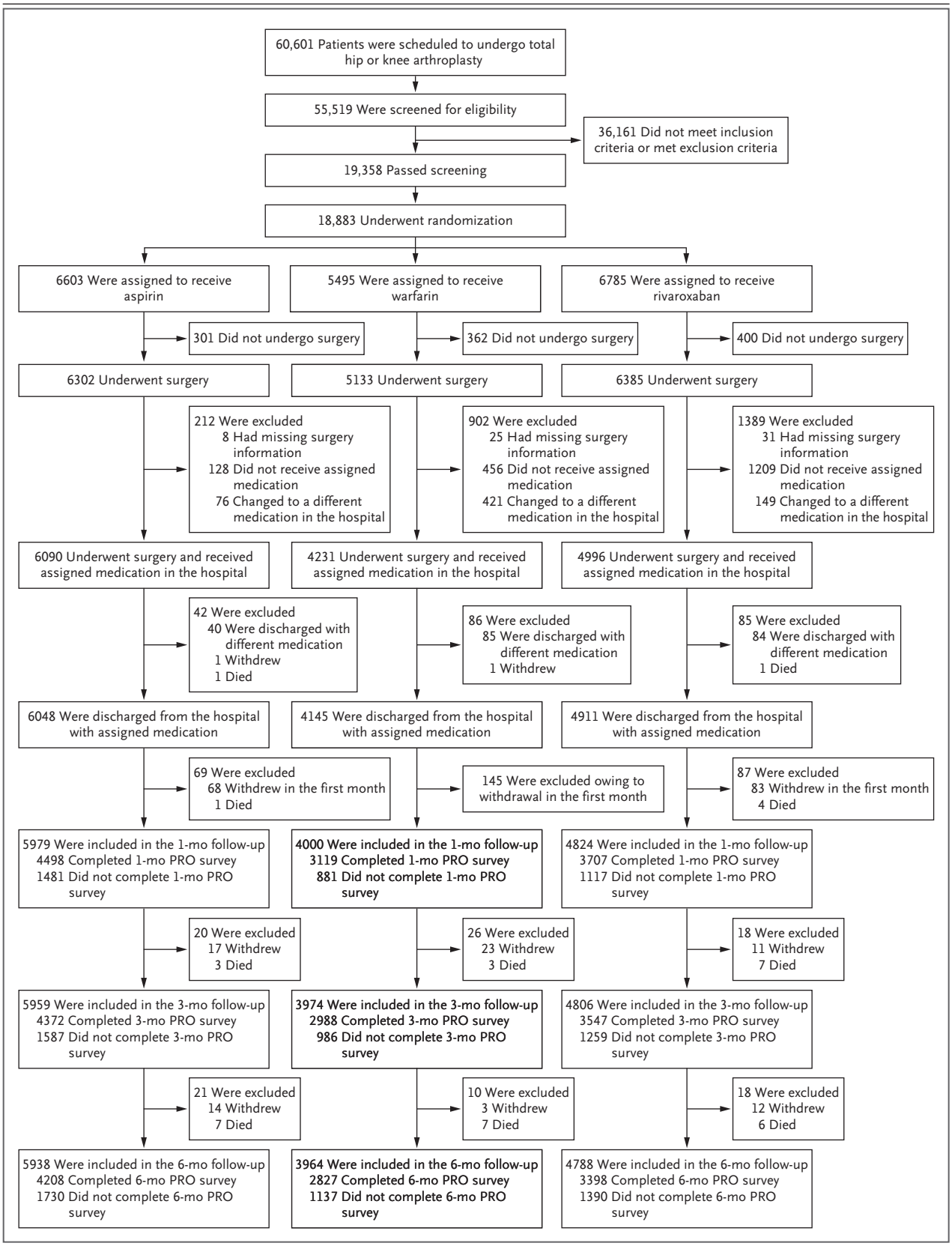
A total of 55,519 patients who were undergoing total hip and knee arthroplasty were screened, of whom 18,883 (34.0%) underwent randomization from December 2016 through November 2024. Participants who did not undergo surgery (1063) or did not receive only the assigned medication in the hospital (2439) were excluded from the primary analysis. Therefore, 15,317 of 17,820 participants (86.0%) who underwent surgery and could be potentially evaluated (of whom 7214 had undergone hip arthroplasty and 8103 knee arthroplasty [with 36.1% and 39.2%, respectively, having undergone revision]) were assigned to receive aspirin (6090 participants), warfarin (4231), or rivaroxaban (4996). The corresponding percentages of the 2648 participants who crossed over from randomly assigned treatments, including those who switched treatment at discharge, were 3.9% (244 participants), 18.7% (962), and 22.6% (1442); the majority of crossovers were attributable to warfarin monitoring or rivaroxaban cost. Participants with missing 6-month data (100 of 6090 participants [1.6%] in the aspirin group, 172 of 4231 [4.1%] in the warfarin group, and 106 of 4996 [2.1%] in the rivaroxaban group) were included in the primary analysis until their withdrawal; 97.5% of living participants had complete data for the primary outcomes (Fig. 1).

The characteristics of the participants at baseline were similar among the three groups. Treatment groups in the primary per-protocol analysis were well-balanced with regard to covariates; 23.1% of the participants took baseline cardioprotective aspirin, and 3.2% had had a recent VTE in the previous 6 months (Table 1). The 4-week postdischarge adherence to the randomized treatment exceeded 90% in all groups. Data on the time in the therapeutic range among participants in the warfarin group were not collected. The randomized sample was representative of the screened population and the general population of patients undergoing total hip and knee arthroplasty (Tables S1 through S4).

EFFECTIVENESS

A primary effectiveness outcome event within 6 months occurred in 77 participants (1.26%) in the aspirin group, in 52 (1.23%) in the warfarin group, and in 47 (0.94%) in the rivaroxaban group. There were 12 deaths (0.20% of the participants) in the aspirin group, 10 (0.24%) in the warfarin group, and 18 (0.36%) in the rivaroxaban

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Figure 1 (facing page). Randomization and Follow-up of the Patients.

Only participants who exclusively received the randomly assigned treatment in the hospital were included in the primary modified per-protocol analysis. Participants who had been discharged with a different treatment had their data censored at discharge, and those who withdrew before 6 months had their data censored at withdrawal. PRO denotes patient-reported outcomes.

group. Causes of death included cardiovascular causes in 12 participants (30%), pulmonary causes in 6 (15%), cancer in 6 (15%), pulmonary embolism in 4 (10%), hemorrhagic causes in 1 (2%), and other causes in 11 (28%) (Table S5). Three deaths due to pulmonary embolism occurred after total hip arthroplasty (in 2 participants in the aspirin group and in 1 in the rivaroxaban group) and 1 after total knee arthroplasty in the rivaroxaban group. The single death due to hemorrhage occurred in a participant in the warfarin group who had not been taking pretrial cardioprotective aspirin and had a hemorrhagic stroke after total hip arthroplasty.

Aspirin did not meet the criterion for noninferiority to either rivaroxaban (primary effectiveness outcome event in 1.24% vs. 0.94% of participants; risk difference, 0.30 percentage points; 95% CI, −0.20 to 0.81; P=0.10) or warfarin (1.24% vs. 1.01%; risk difference, 0.23 percentage points; 95% CI, −0.34 to 0.81; P=0.09) (Table 2). Warfarin was noninferior to rivaroxaban (1.13% vs. 1.10%; risk difference, 0.03 percentage points; 95% CI, −0.57 to 0.63; P=0.01). Intention-to-treat analysis yielded results consistent with those of the per-protocol analysis (Tables S8A, S9, and S10).

The composite effectiveness results in all comparisons were driven by VTE outcomes. In the comparison of aspirin with rivaroxaban, the risks of VTE (1.13% vs. 0.68%) and death (0.15% vs. 0.35%) were directionally opposite; this situation was not seen in the comparison of aspirin with warfarin.

SAFETY

A primary safety outcome event within 6 months occurred in 177 participants (2.91%) in the aspirin group, in 142 (3.36%) in the warfarin group, and in 174 (3.48%) in the rivaroxaban group. Rivaroxaban did not meet the criterion for noninferiority to aspirin (primary safety outcome event in 3.70% vs. 3.02% of the participants; risk difference, 0.68 percentage points; 95% CI, −0.04 to 1.41; P=0.49), and warfarin did not meet the criterion for noninferiority to aspirin (3.65% vs. 2.88%; risk difference, 0.77 percentage points; 95% CI, −0.04 to 1.58; P=0.58) (Table 3). Rivaroxaban also did not meet the criterion for noninferiority to warfarin (3.59% vs. 3.61%; risk difference, −0.02 percentage points; 95% CI, −0.89 to 0.85; P=0.06). Intention-to-treat analysis yielded results consistent with those of the per-protocol analysis (Table S8B).

The overall bleeding risks appeared to be similar in comparisons of rivaroxaban with aspirin (3.20% and 2.35%, respectively) and of warfarin with aspirin (3.16% and 2.16%, respectively). In pairwise comparisons, the risk of nonmajor wound-related bleeding was 1.85% with warfarin and 1.17% with aspirin, and the risk of nonmajor non–wound-related bleeding was 0.72% with rivaroxaban and 0.22% with aspirin.

SUBGROUP ANALYSES ACCORDING TO SURGICAL SITE

No clear evidence of differences between treatment groups was seen in the composite effectiveness and safety outcomes according to whether patients had undergone total hip or knee arthroplasty (Fig. 2). In the comparison of rivaroxaban with aspirin, there was a suggestion of a greater difference in the risk of pulmonary embolism in favor of rivaroxaban among participants who had undergone total hip arthroplasty than among those who had undergone total knee arthroplasty; this difference was not appreciable in the comparison of warfarin with aspirin. Results also suggested the possibility of greater differences in overall bleeding risk between aspirin and either anticoagulant (in both cases, favoring aspirin) in the subgroup of participants who had undergone hip arthroplasty than in the subgroup of those who had undergone knee arthroplasty. These analyses were among multiple comparisons that were performed without adjustment for multiplicity, and numbers for some comparisons were small.

PREOPERATIVE ASPIRIN USE

A post hoc subgroup analysis including 3534 participants who had been taking cardioprotective aspirin before the trial suggested the possibility

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Table 1. Characteristics of the Participants at Baseline (Per-Protocol Population).*

Characteristic	Aspirin (N = 6090)	Warfarin (N = 4231)	Rivaroxaban (N = 4996)
Type of surgery			
Total hip replacement — no. (%)	2853 (46.8)	1980 (46.8)	2381 (47.7)
Revision — no./total no. (%)	1005/2853 (35.2)	735/1980 (37.1)	865/2381 (36.3)
Total knee replacement — no. (%)	3237 (53.2)	2251 (53.2)	2615 (52.3)
Revision — no./total no. (%)	1199/3237 (37.0)	928/2251 (41.2)	1049/2615 (40.1)
Median age (IQR) — yr	64 (57–70)	64 (57–70)	64 (57–71)
Sex — no. (%)			
Female	3330 (54.7)	2507 (59.3)	2950 (59.0)
Male	2760 (45.3)	1724 (40.7)	2046 (41.0)
Median body-mass index (IQR)†	30.7 (26.8–35.3)	31.1 (26.9–35.7)	31.1 (27.0–35.9)
Race or ethnic group — no. (%)‡			
White	4825 (79.2)	3389 (80.1)	3935 (78.8)
Black	905 (14.9)	644 (15.2)	771 (15.4)
Asian	66 (1.1)	30 (0.7)	54 (1.1)
Other	294 (4.8)	168 (4.0)	236 (4.7)
Smoking status — no. (%)			
Never smoked	3389 (55.6)	2345 (55.4)	2804 (56.1)
Current smoking	342 (5.6)	226 (5.3)	270 (5.4)
Former smoking	2359 (38.7)	1660 (39.2)	1922 (38.5)
Alcohol use — no./total no. (%)			
Never	1724/6066 (28.4)	1302/4220 (30.9)	1470/4985 (29.5)
1–4 times per month	2521/6066 (41.6)	1701/4220 (40.3)	2087/4985 (41.9)
>1 time per week	1821/6066 (30.0)	1217/4220 (28.8)	1428/4985 (28.6)
Educational level — no. (%)			
High school diploma or less	1553 (25.5)	1150 (27.2)	1265 (25.3)
Trade or technology school degree or some college	1809 (29.7)	1307 (30.9)	1477 (29.6)
College or graduate degree	2728 (44.8)	1774 (41.9)	2254 (45.1)
Employment status — no. (%)			
Working	2600 (42.7)	1715 (40.5)	2052 (41.1)
Retired, student, or homemaker	2057 (33.8)	1574 (37.2)	1685 (33.7)
Unemployed, disabled, or unknown	1433 (23.5)	942 (22.3)	1259 (25.2)
No. of coexisting conditions according to Charlson Comorbidity Index — no. (%)			
0	3912 (64.2)	2513 (59.4)	3057 (61.2)
1	1538 (25.3)	1181 (27.9)	1357 (27.2)
2	447 (7.3)	374 (8.8)	414 (8.3)
≥3	193 (3.2)	163 (3.9)	168 (3.4)
Recent VTE within past 6 mo — no. (%)§	89 (1.5)	208 (4.9)	193 (3.9)
Pretrial cardioprotective aspirin use — no. (%)			
No	4657 (76.5)	3169 (74.9)	3957 (79.2)
81 mg	1278 (21.0)	942 (22.3)	907 (18.2)
325 mg or other	155 (2.5)	120 (2.8)	132 (2.6)
Tranexamic acid — no. (%)	5860 (96.2)	4042 (95.5)	4790 (95.9)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and VTE venous thromboembolism.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race and ethnic group were reported by the participant.
§ Local-center interpretation of an uncertain VTE diagnosis resulted in some participants being eligible for randomization to the aspirin group if the diagnosis of previous VTE could not be confirmed.

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Table 2. Pairwise Comparisons among Aspirin, Warfarin, and Rivaroxaban for the Primary Composite Effectiveness Outcome and Its Components.*

Event	Comparator 1		Comparator 2		Risk Difference (95% CI)
	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	
		%		%	*percentage points*
	Aspirin		**Rivaroxaban**		
Primary-outcome event	68/5609	1.24 (0.95 to 1.54)	39/4434	0.94 (0.65 to 1.23)	0.30 (–0.20 to 0.81)‡
Death§	8/5609	0.15 (0.05 to 0.25)	14/4434	0.35 (0.17 to 0.53)	–0.21 (–0.41 to 0.00)
VTE	62/5609	1.13 (0.85 to 1.41)	29/4434	0.68 (0.43 to 0.93)	0.45 (0.07 to 0.82)
Pulmonary embolism	24/5609	0.44 (0.26 to 0.61)	12/4434	0.29 (0.13 to 0.45)	0.15 (–0.09 to 0.39)
DVT	38/5609	0.69 (0.47 to 0.91)	17/4434	0.40 (0.21 to 0.59)	0.30 (0.01 to 0.59)
	Aspirin		**Warfarin**		
Primary-outcome event	54/4441	1.24 (0.91 to 1.57)	38/3655	1.01 (0.67 to 1.35)	0.23 (–0.34 to 0.81)¶
Death§	9/4441	0.21 (0.07 to 0.34)	7/3655	0.19 (0.04 to 0.34)	0.02 (–0.18 to 0.22)
VTE	47/4441	1.08 (0.77 to 1.39)	31/3655	0.82 (0.51 to 1.13)	0.26 (–0.18 to 0.69)
Pulmonary embolism	19/4441	0.44 (0.24 to 0.64)	9/3655	0.25 (0.08 to 0.42)	0.19 (–0.07 to 0.45)
DVT	28/4441	0.64 (0.40 to 0.88)	22/3655	0.57 (0.31 to 0.83)	0.07 (–0.28 to 0.42)
	Warfarin		**Rivaroxaban**		
Primary-outcome event	45/3873	1.13 (0.78 to 1.48)	38/3736	1.10 (0.75 to 1.44)	0.03 (–0.57 to 0.63)‖
Death§	9/3873	0.24 (0.08 to 0.40)	14/3736	0.42 (0.21 to 0.63)	–0.18 (–0.45 to 0.08)
VTE	36/3873	0.89 (0.58 to 1.20)	27/3736	0.77 (0.48 to 1.05)	0.13 (–0.30 to 0.55)
Pulmonary embolism	9/3873	0.24 (0.08 to 0.40)	13/3736	0.36 (0.16 to 0.56)	–0.13 (–0.38 to 0.13)
DVT	27/3873	0.66 (0.39 to 0.93)	14/3736	0.40 (0.19 to 0.61)	0.25 (–0.09 to 0.59)

* The primary effectiveness outcome was a composite of death from any cause or symptomatic VTE (pulmonary embolism or deep-vein thrombosis [DVT]). For the effectiveness analyses, aspirin (comparator 1) was hypothesized to be noninferior to warfarin or rivaroxaban (comparator 2) with respect to effectiveness in the prevention of death or symptomatic VTE; warfarin (comparator 1) was hypothesized to be noninferior to rivaroxaban (comparator 2). Pairwise treatment comparisons included only those participants eligible for both treatments. The widths of the confidence intervals for the primary effectiveness outcome have been adjusted for multiplicity; however, those for components of the composite effectiveness outcome have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† The 6-month risk of an event was estimated with the use of a weighted Kaplan–Meier approach; therefore, the percentages may not reflect the ratio of the numerator and the denominator.

‡ Adjusted P=0.10 for noninferiority.

§ Overall, 40 deaths (in 0.26% of the participants) occurred. Causes were classified as cardiovascular in 12 participants (30%), pulmonary in 6 (15%), cancer in 6 (15%), pulmonary embolism in 4 (10%), hemorrhagic causes in 1 (2.5%), and other causes in 11 (27.5%).

¶ Adjusted P=0.09 for noninferiority.

‖ Adjusted P=0.01 for noninferiority.

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Table 3. Pairwise Comparisons among Aspirin, Warfarin, and Rivaroxaban for the Primary Composite Safety Outcome, Its Components, and Nonmajor Non–Wound-Related Bleeding.*

Event	Comparator 1		Comparator 2		Risk Difference (95% CI)
	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	
		%		%	*percentage points*
	Rivaroxaban		**Aspirin**		
Primary safety outcome	157/4434	3.70 (3.13 to 4.27)	167/5609	3.02 (2.56 to 3.47)	0.68 (–0.04 to 1.41)‡
Bleeding	136/4434	3.20 (2.66 to 3.73)	130/5609	2.35 (1.95 to 2.75)	0.84 (0.18 to 1.51)
Major bleeding	64/4434	1.52 (1.15 to 1.90)	63/5609	1.15 (0.86 to 1.43)	0.38 (–0.09 to 0.84)
Nonmajor wound-related bleeding	73/4434	1.69 (1.30 to 2.08)	68/5609	1.22 (0.93 to 1.51)	0.47 (–0.02 to 0.96)
Nonmajor upper GI bleeding	3/4434	0.07 (–0.01 to 0.16)	1/5609	0.02 (–0.02 to 0.05)	0.06 (–0.03 to 0.15)
Myocardial infarction	5/4434	0.13 (0.02 to 0.25)	7/5609	0.12 (0.03 to 0.22)	0.01 (–0.13 to 0.16)
Reoperation for infection	28/4434	0.64 (0.40 to 0.88)	42/5609	0.76 (0.53 to 0.99)	–0.12 (–0.45 to 0.22)
Nonmajor non–wound-related bleeding	30/4434	0.72 (0.46 to 0.97)	12/5609	0.22 (0.10 to 0.34)	0.50 (0.21 to 0.78)
	Warfarin		**Aspirin**		
Primary safety outcome	122/3655	3.65 (3.01 to 4.30)	126/4441	2.88 (2.39 to 3.38)	0.77 (–0.04 to 1.58)§
Bleeding	106/3655	3.16 (2.56 to 3.75)	94/4441	2.16 (1.73 to 2.59)	1.00 (0.26 to 1.74)
Major bleeding	44/3655	1.31 (0.93 to 1.70)	43/4441	0.99 (0.69 to 1.28)	0.33 (–0.16 to 0.82)
Nonmajor wound-related bleeding	63/3655	1.85 (1.39 to 2.31)	51/4441	1.17 (0.85 to 1.49)	0.68 (0.12 to 1.24)
Nonmajor upper GI bleeding	1/3655	0.04 (–0.03 to 0.10)	1/4441	0.02 (–0.02 to 0.07)	0.01 (–0.06 to 0.09)
Myocardial infarction	4/3655	0.11 (0.00 to 0.23)	8/4441	0.18 (0.05 to 0.31)	–0.07 (–0.24 to 0.10)
Reoperation for infection	25/3655	0.76 (0.46 to 1.05)	33/4441	0.76 (0.50 to 1.02)	0.00 (–0.39 to 0.39)
Nonmajor non–wound-related bleeding	11/3655	0.34 (0.14 to 0.54)	6/4441	0.14 (0.03 to 0.25)	0.20 (–0.03 to 0.43)
	Rivaroxaban		**Warfarin**		
Primary safety outcome	128/3736	3.59 (2.98 to 4.20)	129/3873	3.61 (2.99 to 4.22)	–0.02 (–0.89 to 0.85)¶
Bleeding	111/3736	3.10 (2.53 to 3.67)	112/3873	3.12 (2.54 to 3.69)	–0.01 (–0.82 to 0.80)
Major bleeding	51/3736	1.45 (1.06 to 1.84)	48/3873	1.33 (0.95 to 1.71)	0.12 (–0.43 to 0.67)
Nonmajor wound-related bleeding	60/3736	1.66 (1.24 to 2.08)	63/3873	1.76 (1.33 to 2.20)	–0.10 (–0.71 to 0.50)
Nonmajor upper GI bleeding	3/3736	0.09 (–0.01 to 0.18)	1/3873	0.03 (–0.03 to 0.08)	0.06 (–0.05 to 0.17)

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Myocardial infarction	3/3736	0.09 (−0.01 to 0.20)	5/3873	0.13 (0.01 to 0.25)	−0.03 (−0.19 to 0.12)
Reoperation for infection	22/3736	0.60 (0.35 to 0.86)	23/3873	0.66 (0.39 to 0.93)	−0.06 (−0.43 to 0.31)
Nonmajor non–wound-related bleeding	19/3736	0.54 (0.30 to 0.78)	13/3873	0.39 (0.19 to 0.60)	0.15 (−0.17 to 0.46)

* The primary safety outcome was a composite of bleeding (major, according to the International Society on Thrombosis and Haemostasis criteria[24]; nonmajor wound-related bleeding; and upper gastrointestinal [GI] bleeding), reoperation for wound complications, removal of an infected implant, or myocardial infarction. Nonmajor non–wound-related bleeding was a secondary safety outcome. For the safety analyses, warfarin or rivaroxaban (comparator 1) was hypothesized to be noninferior to aspirin (comparator 2) with respect to avoidance of bleeding complications; rivaroxaban (comparator 1) was hypothesized to be noninferior to warfarin (comparator 2).
† The 6-month risk of an event was estimated with the use of a weighted Kaplan–Meier approach; therefore, the percentages may not reflect the ratio of the numerator and the denominator.
‡ P=0.49 for noninferiority.
§ P=0.58 for noninferiority.
¶ P=0.06 for noninferiority.

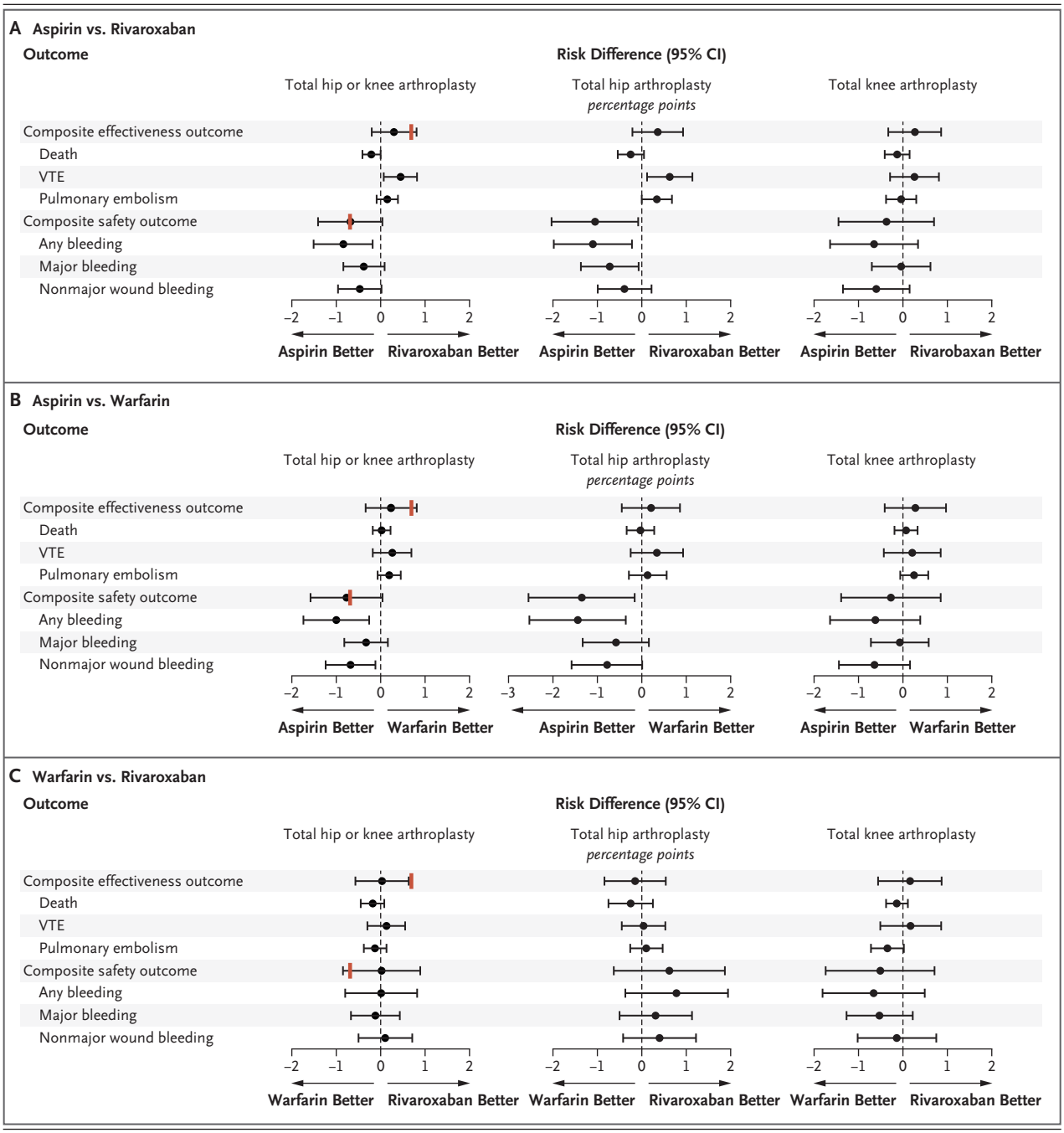
of a higher risk of death (as a specific component of the composite effectiveness outcome) with rivaroxaban than with aspirin or warfarin. In pairwise comparisons, the risk of death was 0.85% (7 participants) in the rivaroxaban group, as compared with 0.17% (2 participants) in the aspirin group, and was 1.37% (9 participants) in the rivaroxaban group, as compared with 0.19% (2 participants) in the warfarin group. This risk difference was not apparent among patients not taking cardioprotective aspirin. The composite safety outcome and its components were also tested post hoc; no apparent between-group differences were observed according to preoperative aspirin use.

DISCUSSION

In this large, multicenter, comparative-effectiveness trial involving patients undergoing elective total hip or knee arthroplasty, we found that aspirin did not meet the prespecified criterion for noninferiority to either rivaroxaban or warfarin for the primary composite effectiveness outcome (death from any cause or VTE). Warfarin was noninferior to rivaroxaban for effectiveness. For the composite safety outcome, neither rivaroxaban nor warfarin met the criterion for noninferiority to aspirin; rivaroxaban also did not meet the criterion for noninferiority to warfarin. Composite safety outcomes were two to three times more common than composite effectiveness outcomes, each with small risk differences.

Our results contrast with those of two smaller trials of total hip and knee arthroplasty (involving 3424 and 5365 participants), which showed that 5 days of treatment with rivaroxaban followed by aspirin was noninferior to treatment with rivaroxaban alone[32] and that aspirin monotherapy was noninferior to aspirin followed by rivaroxaban 5 days after surgery,[33] for the prevention of symptomatic VTE. Those trials used larger noninferiority margins (0.7 percentage points[33] and 1 percentage point[32]), which were equal to the projected overall incidence of VTE. In addition, nonrandomized risk-stratified observational studies that excluded patients at high risk for pulmonary embolism from receiving aspirin have shown low risks of VTE,[16,18] specifically fatal pulmonary embolism,[17] among persons treated with aspirin after total joint arthroplasty. However, in randomized orthopedic trials, aspirin failed tests of

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noninferiority to enoxaparin; anticoagulants were superior to aspirin in preventing VTE after total joint replacement[34] and were associated with lower rates of DVT after fracture.[35]

With respect to components of the composite safety outcome in participants receiving rivaroxaban, nonmajor wound-related bleeding (in 1.69% and 1.66% of the participants, in comparisons with aspirin and warfarin, respectively) and major bleeding (in 1.52% and 1.45%, in comparisons with aspirin and warfarin, respectively) appeared to be less common in this trial, in which the initiation of rivaroxaban was delayed 24 hours after the completion of surgery.

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Figure 2 (facing page). Effectiveness and Safety Outcomes, Overall and According to Surgical Site.

Shown are noninferiority analyses of the primary composite effectiveness and safety outcomes in the overall per-protocol population. Results are also shown in subgroups defined according to surgical site. The primary effectiveness outcome was a composite of death or symptomatic venous thromboembolism (VTE), with VTE defined as pulmonary embolism or deep-vein thrombosis. The primary safety outcome was a composite of bleeding (major, according to the International Society on Thrombosis and Haemostasis criteria[24]; nonmajor wound-related bleeding; and upper gastrointestinal bleeding), reoperation for wound complications, removal of an infected implant, and myocardial infarction. Results for main components are shown for each composite outcome. Results are shown for each of the three randomized head-to-head treatment-group comparisons (aspirin vs. rivaroxaban in Panel A, aspirin vs. warfarin in Panel B, and warfarin vs. rivaroxaban in Panel C). For the effectiveness analyses, aspirin was hypothesized to be noninferior to warfarin or rivaroxaban with respect to effectiveness in the prevention of death or symptomatic VTE; warfarin was hypothesized to be noninferior to rivaroxaban. By contrast, for the safety analyses, warfarin or rivaroxaban was hypothesized to be noninferior to aspirin with respect to avoidance of bleeding complications; rivaroxaban was hypothesized to be noninferior to warfarin. Vertical red lines indicate the noninferiority margin of 0.69 percentage points for each primary composite outcome; note that the direction of comparison is the opposite for the two primary outcomes (effectiveness and safety). The 95% confidence intervals for secondary outcomes (primary-outcome components) and subgroup outcomes according to surgical site (hip or knee) are not adjusted for multiplicity and should not be used in place of hypothesis testing. Numbers of patients in these analyses are provided in Table S6A and S6B.

In previous trials in which rivaroxaban was started 6 hours after surgery,[12-14] persistent drainage was reported in 4 to 5% of participants, and readmission or reoperation was reported in up to 8%. Nonmajor non–wound-related bleeding at sites not near the surgical site, including epistaxis and hematuria, for which no specific treatment is indicated but which can pause or definitively end prophylaxis, appeared to be less frequent with aspirin than with rivaroxaban.

We performed prespecified subgroup analyses according to site of surgery (hip or knee) given current understanding of the pathophysiological characteristics of postoperative thrombogenesis,[19] which suggests the potential for differences in the preferred prophylaxis strategy. Torsional intimal injury (damage to the inner lining of a blood vessel caused by twisting forces) during total hip arthroplasty results in segmental proximal femoral-vein thrombosis with large clots, which have a greater propensity for embolization and hemodynamic compromise.[36,37] In contrast, popliteal-vein occlusion during total knee arthroplasty causes stasis and smaller clots, primarily in the calf, that embolize only after proximal thrombus propagation.[38] Findings from our subgroup analysis suggest the possibility of higher effectiveness of rivaroxaban than aspirin with respect to the risk of pulmonary embolism after total hip arthroplasty than after total knee arthroplasty. However, the number of pulmonary emboli in this trial was small, there was no adjustment for multiplicity, and the trial was not designed to assess noninferiority in subgroups or for components of the primary outcomes — factors that indicate the need for more data according to surgical site to inform recommendations.

Evidence has suggested that combining aspirin with anticoagulants in patients with coronary syndrome or atrial fibrillation is associated with an increased bleeding risk.[39-41] Our post hoc analysis involving participants who had been taking aspirin for cardioprotection before the trial raised the possibility of a higher risk of death among participants taking pretrial aspirin who received rivaroxaban prophylaxis. This finding, which was based on small numbers in a post hoc analysis, may be explained by chance, particularly given the absence of clear differences in bleeding risk according to pretrial aspirin use and the observation that only one death during the trial was attributed to hemorrhage; further study is needed.

Limitations of our trial should be noted. The trial was open-label, although the persons who were adjudicating outcomes were unaware of the treatment assignments. More than 3500 participants who had undergone randomization were excluded from the primary per-protocol analysis; more than 1000 participants never underwent surgery, and 2648 crossed over from the randomly assigned treatment. Because neither cost

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nor monitoring affected adherence to aspirin treatment, there were fewer crossovers from the aspirin group, and the per-protocol aspirin cohort (6090 participants) was 22% larger than the rivaroxaban cohort (4996 participants) and was 44% larger than the warfarin cohort (4231 participants), despite similar initial randomization numbers. Crossovers from treatment assignments compromised the benefits of randomization but reflect the pragmatic comparative-effectiveness design. All the measured covariates, including socioeconomic determinants of health, were well-balanced in the per-protocol cohorts; the percentage of participants lost to follow-up, as well as the percentage of those with at least 90% treatment adherence at 30 days, were similar across the trial groups. Likewise, the results of intention-to-treat analyses appeared to be consistent with the primary per-protocol analyses. Time in the therapeutic range in the warfarin group was not assessed, and thus effectiveness could have been compromised; however, subtherapeutic warfarin would have biased the results toward a finding of noninferiority of aspirin. The number of key coexisting conditions among the trial participants was skewed toward lower medical complexity, as is typical of randomized trials, and may have contributed to the fact that the actual incidence of the composite effectiveness outcome (1.26% with aspirin, 1.23% with warfarin, and 0.94% with rivaroxaban) was lower than the projected incidence (2%). Finally, the Covid-19 pandemic prolonged trial enrollment and made outpatient joint replacement commonplace and anticoagulation monitoring more challenging; as a result, the need for monitoring with warfarin and high rivaroxaban costs compromised adherence to randomization and may affect observed treatment effectiveness.

On the basis of a strict margin for noninferiority, our trial did not show that aspirin was noninferior to warfarin or rivaroxaban with respect to the risk of death or symptomatic VTE. In addition, the trial did not show that warfarin and rivaroxaban were noninferior to aspirin with regard to safety. By providing comparative risk–benefit profiles regarding thrombosis and bleeding for medications used for VTE prophylaxis, these findings can help inform preoperative decision making for patients undergoing elective total hip or knee replacement.

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