ORIGINAL ARTICLE

Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K. Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

ABSTRACT

BACKGROUND

Patients with peripheral artery disease who have undergone lower-extremity revascularization are at high risk for major adverse limb and cardiovascular events. The efficacy and safety of rivaroxaban in this context are uncertain.

METHODS

In a double-blind trial, patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification; major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) was a secondary safety outcome.

RESULTS

A total of 6564 patients underwent randomization; 3286 were assigned to the rivaroxaban group, and 3278 were assigned to the placebo group. The primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan–Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P=0.009). TIMI major bleeding occurred in 62 patients in the rivaroxaban group and in 44 patients in the placebo group (2.65% and 1.87%; hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P=0.07). ISTH major bleeding occurred in 140 patients in the rivaroxaban group, as compared with 100 patients in the placebo group (5.94% and 4.06%; hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P=0.007).

CONCLUSIONS

In patients with peripheral artery disease who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. (Funded by Bayer and Janssen Pharmaceuticals; VOYAGER PAD ClinicalTrials.gov number, NCT02504216.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bonaca at the University of Colorado Anschutz School of Medicine, CPC Clinical Research, 13199 E. Montview Blvd., Suite 200, Aurora, CO 80045, or at marc.bonaca@cpcmed.org.

Drs. Bonaca and Bauersachs contributed equally to this article.

This article was published on March 28, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2000052

It is estimated that more than 200 million people globally have lower-extremity peripheral artery disease, and the incidence is increasing.[1] Although the underlying disease state of atherosclerosis is shared with coronary artery disease and cerebrovascular disease, it is increasingly clear that peripheral artery disease represents a distinct disorder characterized by a high risk of adverse events affecting the limbs, including acute limb ischemia and major amputation, as well as major adverse cardiovascular events.[2,3] Although angiographic studies have detected subclinical coronary disease in a high proportion of patients undergoing vascular surgery, only approximately 30% of these patients were classified as having severe disease.[4] Similarly, in clinical trial populations selected on the basis of symptomatic peripheral artery disease, the prevalence of known symptomatic coronary disease is approximately 30% and a history of myocardial infarction (plaque rupture) is present in only 10 to 20%, despite a high prevalence of smoking, diabetes, and other cardiovascular risk factors.[5]

Limb symptoms that are treated with revascularization frequently develop in patients with peripheral artery disease.[2,3] Such symptoms range from severe claudication, which limits function, to critical limb-threatening ischemia that is treated with revascularization to prevent or limit tissue loss.[6,7] In contrast to coronary intervention and myocardial infarction, peripheral revascularization and critical limb-threatening ischemia are becoming increasingly common.[8] Patients who undergo peripheral revascularization are at high risk for subsequent vascular complications and particularly for acute limb ischemia, with a risk approximately 4 times as high as that among persons who have never undergone revascularization.[9-13] Acute limb ischemia is a particularly serious complication and is associated with long hospitalizations and high incidences of limb loss, disability, and death.[9,10,13,14]

The observation that inhibiting thrombin-mediated activation of platelets with vorapaxar reduced the risk of acute limb ischemia in patients with stable peripheral artery disease indicated that the risk of this complication is modifiable.[2,9] Subsequently, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial showed that rivaroxaban (a selective direct factor Xa inhibitor) at a dose of 2.5 mg twice daily added to aspirin reduced ischemic risk, including the risk of major adverse events affecting the limbs, in a broad population with chronic stable peripheral artery disease enriched for polyvascular disease.[15,16] On the basis of these observations, the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (peripheral artery disease) (VOYAGER PAD) was designed to test the hypothesis that rivaroxaban at 2.5 mg twice daily added to aspirin, as compared with aspirin alone, would reduce the risk of a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes in patients with symptomatic peripheral artery disease who had undergone lower-extremity revascularization.

Methods

Trial Design and Oversight

The design of the trial has been published previously.[17] It was designed and overseen by a collaborative group that included Colorado Prevention Center (CPC) Clinical Research (an academic research organization affiliated with the University of Colorado), the academic executive committee, and the sponsors, Bayer and Janssen Pharmaceuticals. Bayer participated in the trial design, trial oversight, site selection, and the drafting of the manuscript. A contract research organization (Covance) was responsible for site selection, data storage, and data monitoring. The CPC and the executive committee, which included employees of the sponsors, were responsible for trial design and oversight, data interpretation, and the drafting of the manuscript and the decision to submit the manuscript for publication. There were no other funders or providers of nonmonetary support.

The protocol was approved by the relevant ethics committee at each participating site and according to local regulations. An independent data and safety monitoring committee monitored unblinded safety information at specified intervals and performed one unblinded review of efficacy as prespecified in the committee charter. The database is held by CPC Clinical Research, which independently conducted all data analyses for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TRIAL POPULATION

Eligible patients were at least 50 years old and had documented lower-extremity peripheral artery disease, including symptoms, anatomical evidence, and hemodynamic evidence (a full list of inclusion and exclusion criteria is provided in Section B in the Supplementary Appendix, available at NEJM .org). Patients were eligible after a successful revascularization procedure performed within the previous 10 days for symptoms of peripheral artery disease. Patients were excluded if their condition was clinically unstable, if they were at a heightened risk for bleeding, or if they were taking or were anticipated to begin taking prohibited concomitant medications, including long-term treatment with clopidogrel; clopidogrel could be administered for up to 6 months after revascularization at the discretion of the investigator. All patients provided written informed consent.

RANDOMIZATION AND TREATMENT

Eligible patients were randomly assigned in a 1:1 ratio to receive rivaroxaban at a dose of 2.5 mg twice daily or placebo; randomization was performed with a centralized computerized system and was stratified according to the type of index procedure (endovascular [including hybrid] vs. surgical) and according to clopidogrel use or nonuse within the group of patients who underwent an endovascular procedure (Fig. S1 in the Supplementary Appendix). Neither the investigators nor the patients were aware of the treatment assignments. All patients were to receive aspirin at a dose of 100 mg daily as background therapy.

TRIAL OUTCOMES

The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. Secondary efficacy outcomes were tested in a hierarchical fashion, as prespecified, and are listed in Table S1. The principal safety outcome was major bleeding defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification.[18] Major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) and major bleeding as defined by the Bleeding Academic Research Consortium (BARC; grade ≥3b) were assessed as secondary safety outcomes.[19,20] An independent academic clinical events committee adjudicated all deaths, potential ischemic cardiovascular and limb events, and bleeding events in a blinded manner. The definitions of all the trial outcomes have been published previously (see Section C in the Supplementary Appendix).[17]

STATISTICAL ANALYSIS

The trial was event-driven. It was estimated that 1015 primary-outcome events would be required to provide the trial with 90% power to test the primary hypothesis that rivaroxaban would be superior to placebo, with an estimated effect size of 20% (i.e., an approximate estimated hazard ratio [rivaroxaban vs. placebo] of 0.80) and a one-sided level of significance (α) of 0.025 (see Section D in the Supplementary Appendix for further details). A single interim analysis was performed, and the recommendation was to continue the trial as planned; because of the small amount of alpha spending, no adjustment was made for the final efficacy analysis (see the Supplementary Appendix).

The primary composite efficacy outcome was assessed on an intention-to-treat basis in all patients who underwent randomization, regardless of whether they received the trial treatment, in a time-to-event analysis from randomization to the first occurrence of any component of the outcome. The analysis of secondary outcomes was also performed on an intention-to-treat basis and in a hierarchical fashion. Safety outcomes were examined in on-treatment analyses, which included all patients who underwent randomization and received at least one dose of trial medication; these analyses counted the first occurrence of the safety outcome from randomization through 2 days after permanent discontinuation of treatment. An exploratory analysis of the efficacy outcomes in this on-treatment data set was also performed. Subgroups were selected for evaluation of the consistency of the primary efficacy and safety outcomes. The confidence intervals presented in the subgroup analyses have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Event probabilities are expressed as Kaplan–Meier estimates of the cumulative incidence at 3 years after randomization. Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model, stratified according to the type of procedure and according to whether clopidogrel was intended to be used. All reported P values are two-sided and

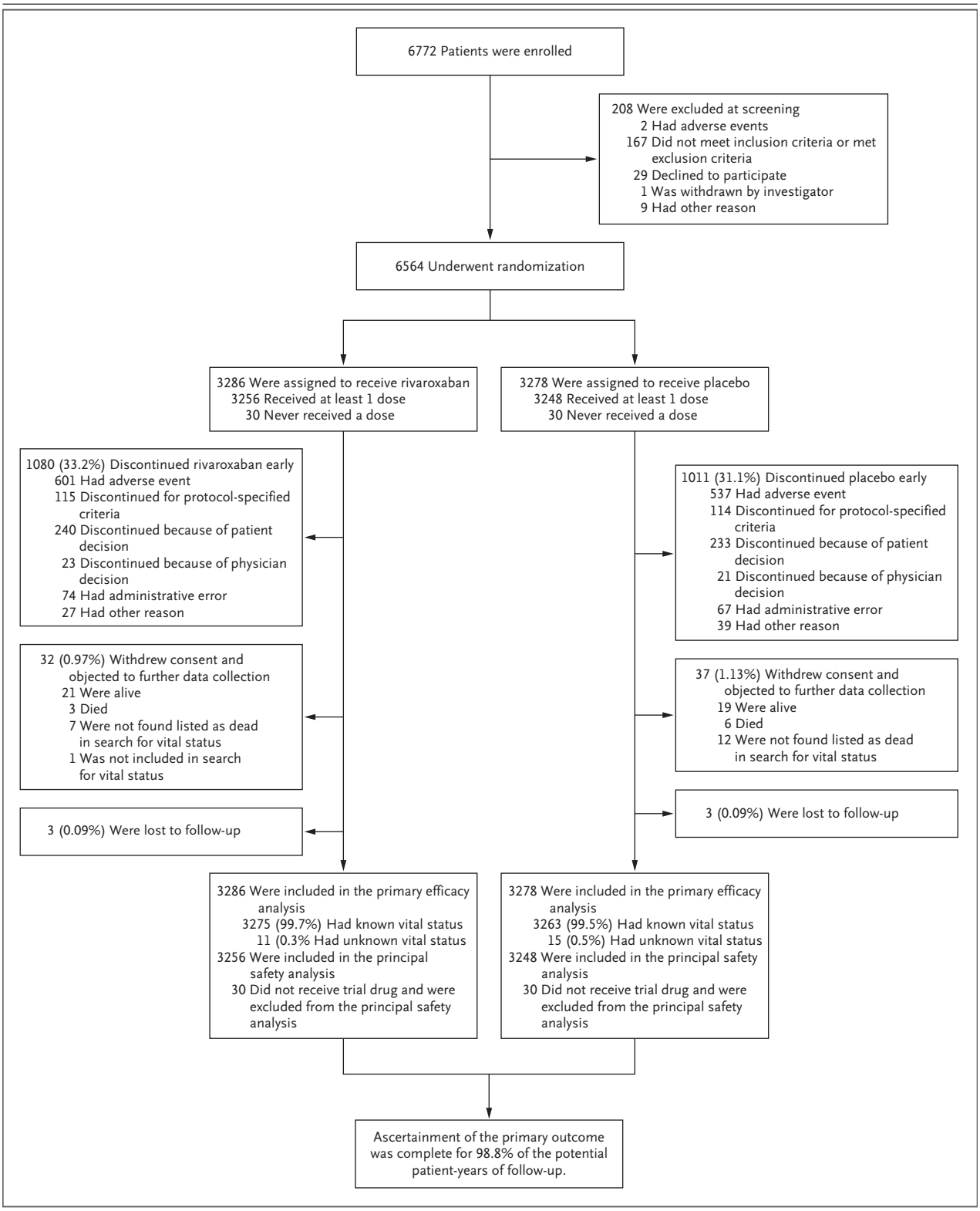

Figure 1 (facing page). Screening, Randomization, and Follow-up.

A total of 37 patients who had been assigned to the rivaroxaban group and 41 patients who had been assigned to the placebo group withdrew their consent for trial procedures but did not object to having data collected, including full ascertainment of efficacy and safety outcomes. For the 32 patients in the rivaroxaban group and the 37 patients in the placebo group who withdrew their consent for trial procedures and objected to further data collection, information on their vital status was sought at the end of the trial, unless a search for such information was prohibited by local restrictions. Premature discontinuation of treatment in accordance with protocol-specified criteria were related to safety exclusions (e.g., receipt of therapeutic anticoagulation).

were obtained with a stratified log-rank test. The plausibility of the proportional-hazards assumption was confirmed by visually comparing the plot of the log of the cumulative hazard between treatments and by adding a treatment-by-time interaction (with time log-transformed) into the model. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

ENROLLMENT AND FOLLOW-UP

A total of 6564 patients underwent randomization from August 2015 through January 2018 at 542 sites in 34 countries (Fig. 1 and Section A in the Supplementary Appendix). The censoring date for the primary analyses was September 8, 2019. The median follow-up period was 28 months (interquartile range, 22 to 34). A total of 6504 patients (99.1%) received at least one dose of trial medication. Of these patients, 1080 (33.2%) in the rivaroxaban group and 1011 (31.1%) in the placebo group discontinued treatment prematurely (Fig. S2). At the end of the trial, data on vital status were available for 6538 patients (99.6%) and were missing for 8 patients and 12 patients in the rivaroxaban and placebo groups, respectively, who had withdrawn consent, as well as 3 patients in each group who were lost to follow-up. Overall, there were 14,752 patient-years of follow-up. Ascertainment of the primary outcome was complete for 98.8% of potential patient-years of follow-up (Fig. 1).

BASELINE CHARACTERISTICS

The baseline characteristics were well balanced between the groups (Table 1). The median age was 67 years, and 26% of the patients were women. Risk factors were common: 40% of patients had diabetes mellitus, 20% had an estimated glomerular filtration rate less than 60 ml per minute per 1.73 m^2 of body-surface area, and 35% were active smokers at randomization. Less than one third of patients (31%) had known coronary disease, and 11% had previous myocardial infarction. The majority of patients had a history of claudication (96%), and the median ankle–brachial index was 0.56. Approximately two thirds of patients had been treated with an endovascular procedure (65%), and one third had been treated surgically (35%) (see Table S2 for procedural details). A total of 1533 patients (23%) had undergone index revascularization for critical limb ischemia (as defined in the Supplementary Appendix). Overall, 80% of patients were taking statin therapy and 63% were taking angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers; 51% were taking clopidogrel.

EFFICACY OUTCOMES

The primary composite outcome occurred in 508 patients in the rivaroxaban group and in 584 patients in the placebo group; the Kaplan–Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85; 95% confidence interval [CI], 0.76 to 0.96; P=0.009) (Fig. 2 and Table 2). The incidences of the first five secondary outcomes in the testing hierarchy were all significantly lower in the rivaroxaban group than in the placebo group, including the incidence of unplanned index limb revascularization for recurrent ischemia (hazard ratio, 0.88; 95% CI, 0.79 to 0.99; P=0.03) (Table 2 and Fig. S3). All-cause mortality was not lower in the rivaroxaban group than in the placebo group (hazard ratio, 1.08; 95% CI, 0.92 to 1.27; P=0.34). Therefore, in accordance with the prespecified hierarchical testing procedure, the assessment of the last secondary outcome (venous thromboembolism) was considered exploratory.

There was no heterogeneity in the efficacy of rivaroxaban plus aspirin as compared with aspirin alone for the primary outcome across major subgroups, including those based on age, sex, and

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Rivaroxaban (N=3286)	Placebo (N=3278)
Median age (IQR) — yr	67.0 (61.0–73.0)	67.0 (61.0–73.0)
Female sex — no. (%)	847 (25.8)	857 (26.1)
Median body-mass index (IQR)†	26.0 (23.3–29.1)	26.0 (23.2–29.1)
Race — no. (%)‡		
White	2647 (80.6)	2656 (81.0)
Asian	484 (14.7)	482 (14.7)
Black	84 (2.6)	71 (2.2)
Other	71 (2.2)	69 (2.1)
Geographic region — no. (%)		
North America	347 (10.6)	347 (10.6)
Western Europe	914 (27.8)	912 (27.8)
Eastern Europe	1301 (39.6)	1298 (39.6)
Asia Pacific	481 (14.6)	480 (14.6)
South America	243 (7.4)	241 (7.4)
Risk factors and coexisting conditions — no. (%)		
Hypertension	2684 (81.7)	2658 (81.1)
Hyperlipidemia	1971 (60.0)	1968 (60.0)
Current smoker	1147 (34.9)	1132 (34.5)
Diabetes mellitus	1313 (40.0)	1316 (40.1)
Estimated GFR <60 ml/min/1.73 m^2	661 (20.1)	666 (20.3)
Symptomatic coronary artery disease	1052 (32.0)	1015 (31.0)
Myocardial infarction	365 (11.1)	349 (10.6)
Known carotid artery disease	282 (8.6)	293 (8.9)
Peripheral artery disease–related history		
Median ankle–brachial index (IQR)	0.56 (0.42–0.67)	0.56 (0.42–0.67)
Previous amputation — no. (%)	194 (5.9)	196 (6.0)
History of claudication — no. (%)	3132 (95.3)	3137 (95.7)
History of critical limb ischemia — no. (%)	999 (30.4)	969 (29.6)
Previous peripheral revascularization — no. (%)	1181 (35.9)	1155 (35.2)
Qualifying revascularization — no. (%)		
Performed for claudication	2521 (76.7)	2504 (76.4)
Performed for critical limb ischemia§	762 (23.2)	771 (23.5)
Endovascular	2153 (65.5)	2140 (65.3)
Surgical	1133 (34.5)	1138 (34.7)
Medications — no. (%)		
Statin	2608 (79.4)	2641 (80.6)
ACE inhibitor or ARB	2096 (63.8)	2063 (62.9)
Aspirin at randomization	3256 (99.1)	3248 (99.1)
Clopidogrel at randomization	1658 (50.5)	1655 (50.5)

* There were no significant differences between groups. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the patient.
§ See the Supplementary Appendix for the definition of critical limb ischemia.

cardiovascular risk factors (Fig. S4). Similarly, there was no heterogeneity on the basis of qualifying symptoms, type of intervention, ankle–brachial index at screening, or the presence of critical limb ischemia at index revascularization. Because some patients stopped taking the trial medication prematurely, we performed an on-treatment efficacy analysis in the safety analysis population, including events from randomization until 2 days after permanent treatment discontinuation. The findings were consistent with those in the intention-to-treat analysis (Table S3).

SAFETY OUTCOMES

The principal safety outcome of TIMI major bleeding during follow-up occurred in 62 patients in the rivaroxaban group and 44 patients in the placebo group, with Kaplan–Meier estimates of the incidence at 3 years of 2.65% and 1.87%, respectively (hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P=0.07) (Table 3). Intracranial hemorrhage occurred in 13 patients in the rivaroxaban group and in 17 patients in the placebo group (hazard ratio, 0.78; 95% CI, 0.38 to 1.61). Fatal bleeding occurred in 6 patients in each group. The composite outcome of intracranial hemorrhage or fatal bleeding occurred in 17 patients in the rivaroxaban group and in 19 patients in the placebo group (hazard ratio, 0.91; 95% CI, 0.47 to 1.76). There was no heterogeneity in the risk of TIMI major bleeding among major subgroups (Fig. S5).

The secondary safety outcome of ISTH major bleeding occurred in 140 patients in the rivaroxaban group and in 100 patients in the placebo group; the Kaplan–Meier estimates of the incidence at 3 years were 5.94% with rivaroxaban and 4.06% with placebo (hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P=0.007) (Table 3). BARC bleeding of grade 3b or greater occurred in 93 patients in the rivaroxaban group and in 73 patients in the placebo group (hazard ratio, 1.29; 95% CI, 0.95 to 1.76; P=0.10). Numbers of adverse events (4423 with rivaroxaban and 4473 with placebo), numbers of patients with at least one serious adverse event that occurred during treatment (948 in the rivaroxaban group and 927 in the placebo group), and numbers of patients who discontinued treatment because of adverse events (20 in the rivaroxaban group and 18 in the placebo group) were similar in the two groups (Tables S4A, S4B, and S5).

We estimate that for every 10,000 patients who

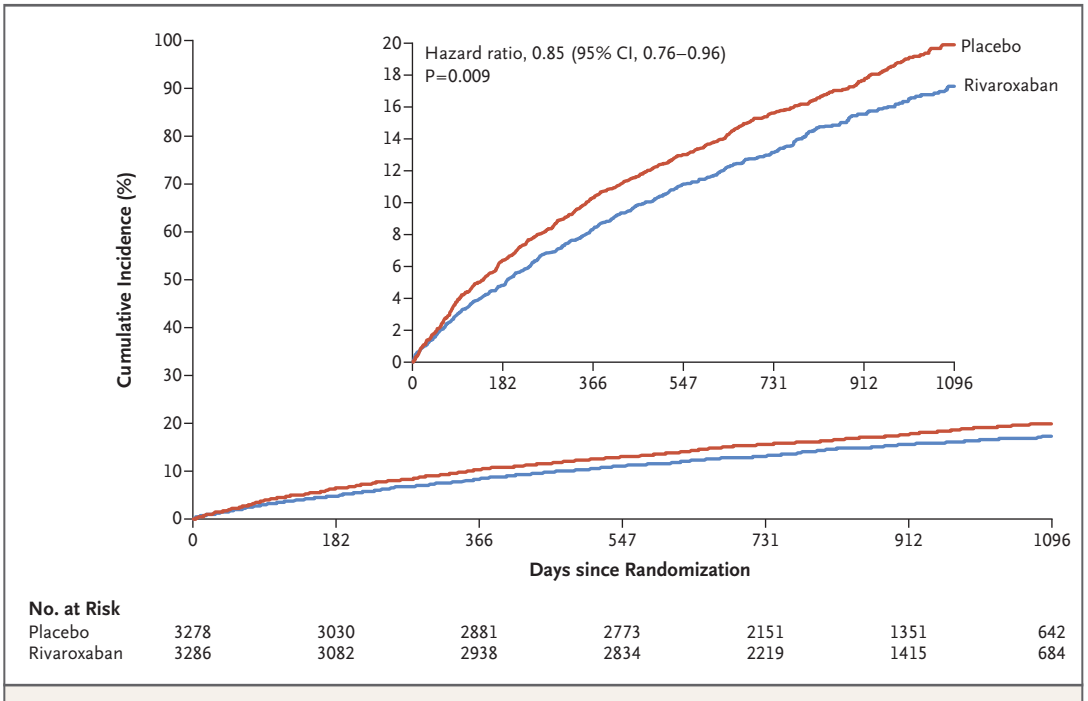

Figure 2. Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The inset shows the same data on an expanded y axis.

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Rivaroxaban (N=3286)		Placebo (N=3278)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K–M Estimate at 3 Yr		
	no.(%)	%	*no. (%)*	%		
Primary efficacy outcome: acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
Acute limb ischemia	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation for vascular causes	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
Myocardial infarction	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
Death from cardiovascular causes	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	
Secondary efficacy outcomes						
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from coronary heart disease	433 (13.2)	14.7	528 (16.1)	18.2	0.80 (0.71–0.91)	<0.001
Unplanned index-limb revascularization for recurrent limb ischemia	584 (17.8)	20.0	655 (20.0)	22.5	0.88 (0.79–0.99)	0.03
Hospitalization for coronary or peripheral event of a thrombotic nature	262 (8.0)	8.7	356 (10.9)	12.1	0.72 (0.62–0.85)	<0.001
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from any cause	614 (18.7)	20.6	679 (20.7)	23.2	0.89 (0.79–0.99)	0.03
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, stroke from any cause, or death from any cause	514 (15.6)	17.5	588 (17.9)	20.1	0.86 (0.76–0.96)	0.01
Death from any cause	321 (9.8)	11.1	297 (9.1)	10.9	1.08 (0.92–1.27)	0.34
Venous thromboembolism	25 (0.8)	0.8	41 (1.3)	1.7	0.61 (0.37–1.00)	

* All efficacy outcomes were analyzed on an intention-to-treat basis. K–M denotes Kaplan–Meier.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=3256)		Placebo (N=3248)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K-M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Principal safety outcome: TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
Intracranial hemorrhage	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
Intracranial or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	
Secondary safety outcomes						
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06	1.42 (1.10–1.84)	0.007
BARC major bleeding†	93 (2.86)	3.86	73 (2.25)	2.92	1.29 (0.95–1.76)	0.10

* Safety analyses included all patients who underwent randomization and had received at least one dose of trial medication. ISTH denotes International Society on Thrombosis and Haemostasis, and TIMI Thrombolysis in Myocardial Infarction.
† Bleeding Academic Research Consortium (BARC) major bleeding is defined as grade 3b or higher.

were treated for 1 year, rivaroxaban at a dose of 2.5 mg twice daily added to aspirin would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events (Fig. S6).

DISCUSSION

Patients with symptomatic peripheral artery disease who have undergone lower-extremity revascularization are at high risk for major adverse limb and cardiovascular events. In this trial, which involved a broad population of patients who had undergone lower-extremity revascularization, nearly 1 in 5 patients in the placebo group had the primary composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes at 3 years. The addition of rivaroxaban at a dose of 2.5 mg twice daily to aspirin reduced this risk by approximately 15%. The benefit was apparent early, with the Kaplan–Meier curves separating at 3 months, was consistent among subgroups, and continued to accrue over time. There was no significant excess in the principal safety outcome of TIMI major bleeding with rivaroxaban. There was a significantly higher incidence of the secondary safety outcome of ISTH major bleeding; however, there was no excess in intracranial hemorrhage or fatal bleeding.

Current practice guidelines recommend aspirin or clopidogrel monotherapy for patients with symptomatic peripheral artery disease, regardless of the clinical setting.[7] Recommendations for more intensive regimens, including dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor or vorapaxar, are given a class IIb recommendation.[6,7] Although the use of dual antiplatelet therapy is common after revascularization for peripheral artery disease, data to support this practice are either observational or extrapolated from randomized trials involving patients with coronary artery disease, in which efficacy has been shown for cardiovascular risk and coronary stent thrombosis rather than for limb outcomes.[6,7,21,22] In reality, however, the risks faced by patients with peripheral artery disease early after revascularization are driven as much or more by acute limb ischemia and major amputation for a vascular cause.[2,9,10,12,14]

Previous trials of antithrombotic therapy after lower-extremity bypass surgery have not shown efficacy and have demonstrated an unacceptable bleeding risk.[21,23] Findings regarding antithrombotic therapy in stable peripheral artery disease have largely been derived from subgroups of patients with coronary disease or broad populations of patients with atherosclerosis that were enriched for and designed to evaluate major adverse cardiovascular events. Severe limb outcomes such as acute limb ischemia, if reported, are typically secondary or exploratory.[2,5,24-26] Our results extend and complement the observations in the Cardio-

vascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, which showed reductions in ischemic risk, including the risk of limb outcomes such as acute limb ischemia, in a broad population of patients with chronic peripheral artery disease enriched for polyvascular disease.[24] Together, these trials show the efficacy of rivaroxaban at a dose of 2.5 mg twice daily added to aspirin in peripheral artery disease from its initiation after the lower-extremity intervention and continuing through long-term prevention.

The effect of rivaroxaban on bleeding in our trial depended on the definition. TIMI major bleeding was chosen as the principal outcome because of the procedural context, in which minor bleeding is common and measures of more severe bleeding (e.g., a hemoglobin threshold of 5.0 g per deciliter) have traditionally been used.[18,21,27] There was no significant difference in the incidence of TIMI major bleeding (fatal bleeding, intracranial hemorrhage, a decrease in hemoglobin level of ≥5 g per deciliter, or hematocrit ≥15%) between the groups. However, there was a significantly higher incidence of the secondary safety outcome of ISTH major bleeding (fatal bleeding, bleeding into a critical site, a hemoglobin level ≥2 g per deciliter, or transfusion of at least 2 units of packed red cells or whole blood) in the rivaroxaban group.

A limitation of the trial is that the percentage of patients who discontinued treatment prematurely, although relatively balanced between the groups, was higher than anticipated. Annualized discontinuation rates in the rivaroxaban group (approximately 14% per year), however, were similar to those observed in other recent trials in stable atherosclerosis and lower than those in some trials in acute coronary syndrome.[5,16,28,29] Nonetheless, the high percentage of patients with premature treatment cessation may have attenuated the benefits observed in the intention-to-treat analysis, as suggested by the on-treatment analysis.

The addition of rivaroxaban at a dose of 2.5 mg twice daily to aspirin in patients with symptomatic peripheral artery disease who had undergone lower-extremity revascularization reduced the incidence of the composite outcome of acute limb ischemia, amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The incidence of the principal safety outcome of TIMI major bleeding was not significantly higher with rivaroxaban plus aspirin than with aspirin alone, but rivaroxaban plus aspirin was associated with a significantly higher incidence of the secondary safety outcome of ISTH major bleeding.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association.

Supported by a grant from Bayer and Janssen Pharmaceuticals. Dr. Bonaca was supported by awards (18SFRN3390085 [BWH-DH SFRN Center] and 18SFRN33960262 [BWH-DH Clinical Project]) from the American Heart Association Strategically Focused Research Network in Vascular Disease.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Dr. Frank Misselwitz for contributing to the conceptualization, guidance, and support of the trial and Dr. Edmond Chen for contributing to the conceptualization, setup, and initial operationalization of the trial.

APPENDIX

The authors' affiliations are as follows: Colorado Prevention Center (CPC) Clinical Research (M.P.B., M.R.N., W.H.C., L.D., N.J., C.N.H., W.R.H.), the Department of Medicine, Division of Cardiovascular Medicine (M.P.B., C.N.H., W.R.H.), the Department of Surgery, Division of Vascular Surgery (M.R.N.), and the Department of Medicine, Division of Endocrinology (W.H.C.), University of Colorado Anschutz Medical Campus, and the Department of Biostatistics and Informatics, Colorado School of Public Health (J.M.K.) — all in Aurora; the Department of Vascular Medicine, Klinikum Darmstadt, Darmstadt, and Center for Thrombosis and Hemostasis, University of Mainz, Mainz (R.M.B.), the Department of Vascular Medicine, Vascular Surgery–Angiology–Endovascular Therapy, University of Hamburg-Eppendorf, Hamburg (E.S.D.), and Bayer, Wuppertal (A.F.P., E.M.) — all in Germany; the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada (S.S.A.); Duke Clinical Research Institute, Division of Cardiology, Duke University, Durham, NC (M.R.P.); the Vascular and Interventional Radiology Department, Careggi University Hospital, University of Florence, Florence, Italy (F.F.); Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine (I.G.); B-A-Z County University Teaching Hospital, Miskolc, Hungary (L.M.); University of Latvia, Pauls Stradins University Hospital, Riga (D.K.K.); ECLA (Estudios Clínicos Latino América), ICR (Instituto Cardiovascular de Rosario), Rosario, Argentina (R.D.); the Division of Angiology, Medical University Graz, Graz, Austria (M.B.); and Janssen Research and Development, Raritan (L.P.H.), and Thrombosis Group Head, Clinical Development, Bayer U.S., Whippany (S.D.B.) — both in New Jersey.

REFERENCES

1. Fowkes FGR, Aboyans V, Fowkes FJI, McDermott MM, Sampson UKA, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 2017;14:156-70.
2. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. Circulation 2013;127:1522-9.
3. Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH Registry. Eur Heart J 2014;35:2864-72.
4. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
5. Hiatt WR, Fowkes FGR, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017;376:32-40.
6. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European Stroke Organization (ESO) Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.
7. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135(12):e726-e779.
8. Agarwal S, Sud K, Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003-2011. J Am Coll Cardiol 2016;67:1901-13.
9. Bonaca MP, Gutierrez JA, Creager MA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). Circulation 2016;133:997-1005.
10. Hess CN, Huang Z, Patel MR, et al. Acute limb ischemia in peripheral artery disease. Circulation 2019;140:556-65.
11. Hess CN, Rogers RK, Wang TY, et al. Major adverse limb events and 1-year outcomes after peripheral artery revascularization. J Am Coll Cardiol 2018;72:999-1011.
12. Jones WS, Baumgartner I, Hiatt WR, et al. Ticagrelor compared with clopidogrel in patients with prior lower extremity revascularization for peripheral artery disease. Circulation 2017;135:241-50.
13. Hess CN, Wang TY, Weleski Fu J, et al. Long-term outcomes and associations with major adverse limb events after peripheral artery revascularization. J Am Coll Cardiol 2020;75:498-508.
14. Anand SS, Caron F, Eikelboom JW, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS Trial. J Am Coll Cardiol 2018;71:2306-15.
15. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319-30.
16. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9-19.
17. Capell WH, Bonaca MP, Nehler MR, et al. Rationale and design for the Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). Am Heart J 2018;199:83-91.
18. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
19. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
20. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
21. Belch JJ, Dormandy J, Biasi GM, et al. Results of the randomized, placebo-controlled Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral Arterial disease (CASPAR) trial. J Vasc Surg 2010;52:825-33.
22. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
23. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (the Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. Lancet 2000;355:346-51.
24. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:219-29.
25. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol 2016;67:2719-28.
26. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309-20.
27. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
28. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.
29. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297-309.