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Brief Title: Total Event Reduction in VOYAGER PAD

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Affiliations:

1. Department of Vascular Medicine, Klinikum Darmstadt, Darmstadt, and Center for Thrombosis and Hemostasis, University of Mainz, Mainz
2. CPC Clinical Research, Aurora CO
3. Division of Angiology, Medical University Graz, Austria
4. Ivano-Frankivsk National Medical University, Ukraine
5. Department of Vascular Medicine, Vascular Surgery–Angiology–Endovascular Therapy, University of Hamburg-Eppendorf, Hamburg, Germany
6. Department of Surgery, Division of Vascular Surgery, University of Colorado School of Medicine, Aurora, CO
7. Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada
8. Duke Clinical Research Institute, Division of Cardiology, Duke University, Durham, NC
9. Department of Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora, CO
10. Department of Medicine, Division of Endocrinology, University of Colorado School of Medicine, Aurora, CO
11. Department of Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora, CO
12. Bayer AG Research & Development, Pharmaceuticals, Wuppertal, Germany
13. Janssen Research and Development, Raritan, NJ
14. Thrombosis & Vascular Medicine, Clinical Development, Bayer U.S., Whippany, NJ
15. Department of Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora CO; CPC Clinical Research, Aurora, CO
16. Department of Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora CO; CPC Clinical Research, Aurora, CO

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Corresponding Author:
Marc P. Bonaca MD MPH
Professor of Medicine/Cardiology
University of Colorado Anschutz School of Medicine
CPC Clinical Research
13199 E. Montview Blvd, Suite 200, Aurora, CO 80045
Phone (303) 991-7406; Fax (303) 860-1288
marc.bonaca@cpcmed.org

Twitter Handle @MarcBonaca

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ABSTRACT

BACKGROUND: Patients with peripheral artery disease (PAD) undergoing lower extremity revascularization (LER) are at high risk of major adverse limb and cardiovascular events. VOYAGER PAD demonstrated that rivaroxaban 2.5 mg twice daily reduced first events by 15%. The benefit of rivaroxaban on total (first and subsequent) events in this population is unknown.
OBJECTIVES: To evaluate the total burden of vascular events in PAD patients after LER and the efficacy of low dose rivaroxaban on total events.
METHODS: VOYAGER PAD randomized PAD patients undergoing LER to rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone. The primary endpoint was time to first event of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, or CV death. The current analysis considered all events (first and subsequent) for components of the primary endpoint as well as additional vascular events including peripheral revascularizations and venous thromboembolism. Hazard ratios were estimated by marginal proportional hazards models.
RESULTS: Among 6564 randomized there were 4714 total first and subsequent vascular events including 1614 primary endpoint events and 3100 other vascular events. Rivaroxaban reduced total primary endpoint events (HR 0.86,95% CI 0.75-0.98; p=0.02) and total vascular events (HR 0.86,95% CI 0.79-0.95; p=0.003). An estimated 4.4 primary and 12.5 vascular events/100 participants were avoided with rivaroxaban over three years.
CONCLUSIONS: Symptomatic PAD patients undergoing LER have a high total event burden which is significantly reduced with rivaroxaban. Total event reduction may be useful metric to quantify the efficacy of rivaroxaban in this setting.

CONDENSED ABSTRACT: VOYAGER PAD randomized PAD patients after revascularization to rivaroxaban plus aspirin or aspirin alone and demonstrated that rivaroxaban reduced first primary endpoints events (acute limb ischemia, major vascular amputation, myocardial infarction, ischemic stroke, or CV death) by 15%. Among 6564 randomized there were 4714 total first and subsequent vascular events (1614 primary and 3100 other vascular events). Rivaroxaban significantly reduced total primary endpoint and total vascular events each by ~15% translating to an estimated 4.4 primary and 12.5 vascular events/100 participants avoided over three years demonstrating both the high risk in this population and total magnitude of benefit.

KEYWORDS: Peripheral artery disease, revascularization, acute limb ischemia, rivaroxaban

ABBREVIATIONS AND ACRONYMS
CI = confidence interval
HR = hazard ratio
PAD = peripheral artery disease
LER = lower extremity revascularization

CLINICAL TRIAL: ClinicalTrials.gov: NCT02504216

Patients with peripheral artery disease (PAD) are at a heightened risk for major adverse limb and cardiovascular events.(1,2) A history of lower extremity revascularization has been associated with a significantly higher risk of adverse limb events, even years after the procedure.(3,4) More recently, the risk profile of PAD patients acutely after revascularization has been described showing a markedly higher risk of adverse limb outcomes early after intervention.(5)

The VOYAGER PAD study demonstrated that at 3 years, approximately 20% of patients undergoing LER experienced a first adverse limb or cardiovascular event event inspite of treatment with aspirin in all patients, statins in 80% and clopidogrel in half of the patients.(6) The addition of rivaroxaban 2.5 mg twice daily plus aspirin versus aspirin alone reduced first events by approximately 15% translating into a number needed to treat (NNT) to prevent a first event of 39 at 3 years. These findings, however, did not report the incidence of subsequent events and the effect of rivaroxaban on reduction of total events. Therefore, the rate of total (i.e., first and potentially subsequent) events in this population and the benefit of rivaroxaban on total events is unknown.

In a pre-specified analysis from VOYAGER PAD, we investigated the number of first and total events in PAD patients undergoing LER. In addition, we evaluated the composition of events including all limb and cardiovascular events. Finally, we then evaluated the efficacy and safety of rivaroxaban on first and total events.

Methods

Population

Details of the study design (7) and primary efficacy and safety results (6) have been published previously. The study was a multinational trial and each site obtained the relevant

institutional review board and ethics approvals. Qualifying patients had symptomatic PAD defined by abnormal ankle-brachial index (ABI) ≤ 0.80 or toe-brachial index (TBI) ≤ 0.60 (in those without a prior history of LER) and a technically successful revascularization procedure within the past 10 days to treat infrainguinal PAD. Key exclusion criteria included planned long-term dual antiplatelet therapy with clopidogrel (> 6 months), requirement for therapeutic anticoagulation, recent acute limb ischemia (within 2 weeks of the qualifying revascularization) or acute coronary syndrome, medical conditions that could increase the risk of major bleeding, significantly impaired renal function at baseline (eGFR < 15mL/min/1.73m2), and any documented history of intracranial hemorrhage, stroke or transient ischemic attack. Randomization in a 1:1 ratio to treatment with rivaroxaban 2.5 mg twice daily or matching placebo was performed with 6564 patients meeting study entry criteria. All patients received aspirin 100 mg daily as background therapy and clopidogrel was allowed at the treating physician's discretion. Follow-up visits were scheduled 1, 3, and 6 months after randomization and every 6 months thereafter until approximately 1015 participants experienced a first primary efficacy endpoint, after which surviving participants had a final end-of-study visit. A total of 1092 first primary outcome events were included in the primary analysis.

Endpoints

The primary efficacy outcome of VOYAGER PAD was time to first occurrence of acute limb ischemia, major amputation for vascular causes, non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death, including death of unknown etiology. Additional prespecified categories of vascular events recorded in the trial included subsequent peripheral revascularizations of both index and contralateral leg and venous thromboembolic events. Non-vascular deaths were also recorded during follow-up. Definitions for each event have been

published.(7) The current analysis evaluating total (first and subsequent events) was pre-specified prior to database lock. Events included in the primary analysis of the present report were total (i.e., first and subsequent) primary endpoint events, total other vascular events (peripheral revascularizations and venous thromboembolism), and total vascular events (total primary endpoint events plus total other vascular events). Additional analyses of total events were by category of event as denoted in **Table 1**. Except for peripheral revasvularizations and venous thromboembolism, all events included in the analyses were adjudicated by an independent committee blinded to treatment assignment. Peripheral revascularizations and venous thromboembolism were reported by investigators blinded to treatment assignment on a specific case report form.

Statistical Methods

We applied a marginal proportional hazards model that allows for the possibility of multiple vascular events within a given participant while treating non-vascular death as a competing terminal event. A robust sandwich variance estimate for the estimated standard error of the log hazard ratio was used to account for the dependence of event times within individual patients. Treatment effects on total primary and total vascular events are summarized by hazard ratios (HRs), corresponding 95% confidence intervals (CIs), and p-values. Treatment effects on additional categories of total vascular events were estimated in separate models; vascular deaths not included in a given category were also treated as competing terminal events. Mean cumulative functions were used to estimate, by treatment group, rates of total primary endpoint events and total vascular events in the presence of competing non-vascular death. Because some patients randomized to rivaroxaban were not receiving study treatment at the time of events, *post hoc* sensitivity analyses were conducted that included rivaroxaban exposure as a time-varying

covariate. In these analyses, events in the rivaroxaban group that occurred after a given patient's last dose of study drug were attributed to placebo.

Continuous variables are expressed as median (quartile 1, quartile 3) whereas categorical variables are expressed as counts and percentages. Comparisons of baseline demographics and clinical characteristics of participants grouped by categories of event frequencies were by Wilcoxon rank sum tests for continuous variables and Chi-square or Fisher's exact tests (where appropriate) for categorical variables. Incidence rates were calculated as number of events per 100 patient-years of follow-up with corresponding exact 95% confidence intervals. For all analyses, p-values <0.05, 2-tailed, were considered statistically significant, with no adjustment for multiple testing.

All analyses were conducted according to intention-to-treat, including all participants and events from randomization until the common study end date of 08 September 2019. Analyses were performed in SAS 9.4 and R 3.5.

Results

First and Total Events

Patients were followed for survival for a median of 2.5 (2.0, 3.0) years. Exposure to randomized treatment as a percentage of follow-up for survival was 79.6% and 81.0% for the rivaroxaban and placebo groups, respectively. A total of 2,114 (32%) of the 6,564 patients randomized experienced a first vascular event that was non-fatal, including 1,012 patients in the rivaroxaban group and 1,102 in the placebo group. Among these 2,114 patients, 1,694 (80%), including 794 (78.5%) in the rivaroxaban group and 900 (81.7%) in the placebo group, were receiving randomized treatment at the time of the event. In addition, all 1,694 of these patients

who experienced a first non-fatal event on treatment continued randomized treatment after their first event, thus allowing treatment to potentially influence the occurrence of subsequent events. Baseline characteristics by groups defined by event frequency categories are summarized in Supplemental Table 1. Participants with at least one event differed from patients with no events during the study in most characteristics, including higher rates of comorbidities such as hypertension, diabetes, and kidney disease. Comparing groups with at least one event, patients with multiple events versus a single event were more likely to have prior revascularization, a long (>15 cm) target lesion length for the qualifying revascularization, treatment with atherectomy, and treatment with placebo during the study.

Total Events by Type

Types and counts of total vascular events and non-vascular deaths after randomization by treatment assignment are shown in **Table 1**. The total number of primary endpoint events (1614) was 48% greater than first primary events (1092). Peripheral revascularization was the most common type of event, comprising 64% of total vascular events. Of the peripheral revascularizations, 1951 (64.3%) occurred in the index limb and 1083 (35.7%) occurred in the contralateral limb. In addition, 705 of total peripheral revascularizations occurred in the 2185 patients treated with index surgical revascularization and 2329 occurred in the 4379 patients treated with index endovascular revascularization. Competing non-vascular deaths were relatively infrequent and equally distributed between the treatment groups.

The distributions of vascular events by ordinal event, further grouped by major adverse cardiovascular events (MACE), major adverse limb events (MALE), other peripheral events, or non-vascular death are summarized in **Table 2**. There were 4714 total vascular events, more than double the number of first events (n=2301). The number of participants with a first event

includes 872 who had a primary efficacy endpoint and 1429 who had a vascular event other than the primary efficacy endpoint. Furthermore, although a majority of participants did not experience an event during the study, a significant subset (1092 of the 2114 participants with a nonfatal first event, and 16.6% of the total study population) experienced more than one vascular event. In total, a similar number of MACE events occurred in each treatment group (426 for rivaroxaban, 430 for placebo), so that the treatment group difference in total events was primarily due to peripheral events. Normalizing for duration of follow-up, the incidence rates for second and third events was a multiple of the first event rate for both treatment groups.

To explore possible differences in the risk for a second vascular event by type of first non-fatal event, the incidence of second events by subcategory of first event are presented in **Figure 1.** While the incidence of second events among patients with a first non-fatal event was high overall (**Table 2**), the majority (60%) of second events were experienced by patients who experienced a first peripheral revascularization. Additionally, patients with a first MALE event had a high rate of subsequent peripheral revascularization. Specifically, among 148 patients in the rivaroxaban group and 203 patients in the placebo group with a first MALE, 96 (64.9%) and 138 (68.0%) patients, respectively, had peripheral revascularization as a second event.

Efficacy of Rivaroxaban for Total Vascular Events

Except for vascular death, participants randomized to rivaroxaban had numerically fewer vascular events of every type (Table 1). Overall, there were 342 fewer total vascular events with rivaroxaban (2186 events for rivaroxaban, 2528 events for placebo), including 61 fewer first vascular events (1120 events for rivaroxaban versus 1181 for placebo), and 281 fewer subsequent vascular events (**Figure 1**). Thus, analysis of first events reflects only 18% of the total event reduction associated with rivaroxaban treatment over a median of 2.5 years.

The cumulative incidence functions for total primary endpoint events and total vascular events over time by treatment group and the associated treatment hazard ratios are shown in the **Central Illustration**. In the placebo group, over three years, the estimated number of events was 30.3 for total primary endpoint events and 88.4 for total vascular events per 100 patients. Rivaroxaban modified this burden by reducing total primary endpoint events by 14% (HR 0.86, 95% CI 0.75 to 0.98; p=0.02) and total vascular events by 14% (HR 0.86, 95% CI 0.79 to 0.95; p=0.003). *Post hoc* sensitivity analyses treating rivaroxaban exposure as a time-varying covariate were consistent with the intention-to-treat results, revealing a more robust effect estimate for the benefit of rivaroxaban versus placebo for total primary endpoint events (HR 0.42, 95% CI 0.37 – 0.49, p<0.0001) and total vascular events (HR 0.63, 95% CI 0.57 – 0.69, p<0.0001). These results reflect the fact that 903 (41.3%) of the 2186 vascular events in the rivaroxaban group occurred after a given patient's last dose of study drug.

Figure 2 displays treatment hazard ratios and estimated three-year incidences by treatment group for total vascular results overall and by event type, including the expected number of events over three years per 100 participants for each treatment group. Over three years, an estimated 4.4 primary and 12.5 vascular events per 100 participants were avoided with rivaroxaban treatment. In terms of individual event types, rivaroxaban significantly reduced total acute limb ischemia, peripheral revascularization, and venous thromboembolic events, consistent with the findings in **Table 2**. Regarding peripheral revascularizations, the benefit of rivaroxaban vs. placebo was consistent for subsets of events defined by limb (index HR 0.83, 95% CI 0.73 – 0.96; contralateral HR 0.93, 95% CI 0.79 – 1.08) and for patient subgroups defined by mode of index revascularization (surgical: 346 events for rivaroxaban, 359 events for placebo, HR 0.98,

95% CI 0.80 – 1.20; endovascular: 1070 events for rivaroxaban, 1259 events for placebo, HR 0.84, 95% CI 0.74 – 0.96, p-interaction 0.22).

Discussion

The current analysis demonstrates several novel findings. First, PAD patients undergoing LER are at an extremely high risk for limb and cardiovascular events with a significantly greater burden when considering total rather than first events. Second, the most significant burden of risk is driven by vascular limb outcomes with recurrent peripheral revascularization being a particularly frequent event. Finally, the magnitude of absolute benefit of rivaroxaban 2.5 mg twice daily plus aspirin versus aspirin alone in this population is even greater when considering total vascular events.

Patients with atherosclerotic vascular disease, particularly those that suffer an event, are at risk for recurrent events.(8) Prior analyses in patients with acute coronary syndrome have reported rates of total events which are largely driven by recurrent coronary events and coronary revascularization.(9,10) For example, in patients with acute coronary syndrome, the majority of vascular events and absolute reduction of events occurred in the coronary territory;(9-12) similar patterns have been observed in patients with cerebrovascular disease.(13) Such analyses in large PAD trials have not been reported previously.(14) In this context the current results are notable in that the incidence of total events was high including 4714 events in 6564 patients. This volume of total events is as great or greater than those observed in coronary popultations.(10) This observation highlights the need to consider total events in PAD populations particularly when considering the total burden and costs of disease.

In addition, and in contrast to coronary cohorts, the distribution of events is distinct and is driven by peripheral revascularizations and adverse limb outcome rather than major adverse

cardiovascular events. For example, there were a total of 758 acute limb ischemia or major amputation events, greatly outweighing myocardial infarctions (322) and ischemic strokes (161). These findings underscore the importance of collecting and considering adverse limb outcomes in trials including PAD patients, including those randomizing patients after revascularization.

Finally, the benefits of rivaroxaban described in the primary results of VOYAGER PAD reported a number needed to treat of 39 to prevent a first event at 3 years.(6) The current analysis demonstrates that the benefit of rivaroxaban was consistent for patients that went on to have second, third, fourth and more events. In other words, approximately 2.6 first primary endpoint events would be prevented per 100 patients initiated on treatment while an estimated 4.4 total primary and 12.5 total vascular events would be prevented in the overall population. Patients at especially high risk of subsequent events, such as those with a history revascularization prior to the index procedure and those with longer target lesions (>15 cm), would be anticipated to have even greater benefit.This continued benefit underscores the importance of long-term preventive strategies and that first events underestimate the total benefit. For example, in the primary analysis, a difference of 76 primary efficacy events was reported by treatment group in contrast to the 342 (~4.5 fold) total vascular events reported in the current manuscript. This finding may be of use to clinicians determining the impact of a rivaroxban strategy in PAD patients undergoing LER and underscore the importance of continuing preventive therapies in patients who experience a non-fatal event. Benefits must be weighed against bleeding risk. In VOYAGER PAD, rivaroxaban increased TIMI major bleeding by 43% (62 events with rivaroxaban versus 44 events with placebo, difference of 18 events). The difference in ISTH major bleeding, a more sensitive measure, was similar in relative terms (42% increase) but with 140 events with rivaroxaban versus 100 with placebo (difference of 40 events).

Limitations

There are several limitations to the current analysis. Although this total events analysis was pre-specified prior to database lock, the primary efficacy outcome was time to first event and therefore the current findings should be considered complimentary. Secondly, more patients randomized to rivaroxaban prematurely terminated treatment relative to placebo and therefore estimates of effects may underestimate those in patients taking therapy. Finally, the current analysis does not assign weights to individual outcomes. While components of the primary outcome are generally considered irreversible harm events, the need for recurrent revascularization may be considered less severe. Therefore, the results should be considered carefully in the context of bleeding.

Conclusions

Patients with PAD undergoing LER are at high risk of adverse limb and cardiovascular events, with a particularly high burden when considering total events inspite of standard available medical therapy. The risk profile in patients with symptomatic PAD is dominantly driven by adverse limb outcomes, particularly after LER, including acute limb ischemia, major vascular amputation and recurrent revascularization. Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone reduces first and subsequent adverse limb and cardiovascular events with an even greater total benefit when considering all events.

Clinical Perspectives

Competency in Patient Care and Procedural Skills: Compared to aspirin alone, the combination of rivaroxaban plus aspirin reduces total vascular events, and particularly recurrent ischemic limb events, in patients with peripheral artery disease (PAD) who have undergone lower extremity revascularization, but increases the risk of bleeding.

Translational Outlook: Further research is needed to identify patient subgroups at highest ischemic risk who gain the greatest benefit from dual pathway inhibitor antithrombotic therapy.

References

1. Bhatt DL, Eagle KA, Ohman EM et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7.

2. Bonaca MP, Scirica BM, Creager MA et al. Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50. Circulation 2013;127:1522-9, 1529e1-6.

3. 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 degrees P-TIMI 50). Circulation 2016;133:997-1005.

4. Qamar A, Morrow DA, Creager MA et al. Effect of vorapaxar on cardiovascular and limb outcomes in patients with peripheral artery disease with and without coronary artery disease: Analysis from the TRA 2 degrees P-TIMI 50 trial. Vasc Med 2020;25:124-132.

5. 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.

6. Bonaca MP, Bauersachs RM, Anand SS et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med 2020;382:1994-2004.

7. 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.

8. Bonaca MP, Storey RF, Theroux P et al. Efficacy and Safety of Ticagrelor Over Time in Patients With Prior MI in PEGASUS-TIMI 54. J Am Coll Cardiol 2017;70:1368-1375.

9. Murphy SA, Cannon CP, Blazing MA et al. Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. J Am Coll Cardiol 2016;67:353-361.

10. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. J Am Coll Cardiol 2009;54:2358-62.

11. Szarek M, Bittner VA, Aylward P et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. Eur Heart J 2020;41:4245-4255.

12. Szarek M, White HD, Schwartz GG et al. Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events: The ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019;73:387-396.

13. Szarek M, Amarenco P, Callahan A et al. Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories: The SPARCL Trial. J Am Coll Cardiol 2020;75:2110-2118.

14. Belch JJ, Dormandy J, Committee CW 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, 833 e1-2.

Figure Legends

Figure 1. Incidence of Second Vascular Event by Type of First Non-fatal Vascular Event. The majority (60%) of second events were experienced by patients who experienced a first peripheral revascularization. MACE = major adverse cardiovascular event; MALE = major adverse limb event.

Figure 2. Distribution of First and Subsequent Vascular Events. There were 342 fewer total vascular events with rivaroxaban versus 61 fewer first vascular events. MACE = major adverse cardiovascular event; MALE = major adverse limb event.

Figure 3. Treatment Effects on Total Vascular Events by Event Type. Hazard ratios, 95% confidence intervals, and p-values from marginal proportional hazards models with death not included in a given category treated as a competing terminal event. CI = confidence interval; HR = hazard ratio.

Central Illustration. Mean Cumulative Functions for Total Primary Events and Total Vascular Events. Accrual of events per 100 participants. The estimated number of events per 100 participants in the rivaroxaban and placebo groups at 3 years were 25.9 and 30.3 for total primary events and 75.9 and 88.4 for total vascular events, respectively. Rivaroxaban reduced total primary events by 14% (HR 0.86, 95% CI 0.75 to 0.98; p=0.02) and total vascular events by 14% (HR 0.86, 95% CI 0.79 to 0.95; p=0.003). Hazard ratios, 95% confidence intervals, and p-values from marginal proportional hazards models with non-vascular death as a competing terminal event. CI = confidence interval; HR = hazard ratio.

Table 1. Categories of Total Events

Event	Rivaroxaban (n = 3286)	Placebo (n = 3278)	Total (n = 6564)
Total Vascular	**2186**	**2528**	**4714**
Primary endpoint events	745	869	1614
Acute limb ischemia	*202*	*306*	*508*
Major amputation for vascular causes	*117*	*133*	*250*
Non-fatal myocardial infarction	*152*	*170*	*322*
Non-fatal ischemic stroke	*75*	*86*	*161*
Cardiovascular Death	*199*	*174*	*373*
Other Vascular events	1441	1659	3100
Peripheral revascularization[a]	*1416*	*1618*	*3034*
Index limb	*894*	*1057*	*1951*
Contralateral limb	*522*	*561*	*1083*
Venous thromboembolic event[a]	*25*	*41*	*66*
Non-vascular death	**122**	**123**	**245**

Values are n.

[a]Investigator-reported; not subject to adjudication by independent committee.

Table 2. Distribution of First and Subsequent Vascular Events and Non-Vascular Death

	Rivaroxaban (n = 3286)		Placebo (n = 3278)	
	n/N (%)	**Events per 100 p-y (95% CI)**	**n/N (%)**	**Events per 100 p-y (95% CI)**
First Event				
Any vascular	1120/3286 (34.1)	17.4 (16.4, 18.5)	1181/3278 (36.0)	18.7 (17.6, 19.7)
MACE[a]	263/3286 (8.0)	4.1 (3.6, 4.6)	258/3278 (7.9)	4.1 (3.6, 4.6)
Fatal	*108/3286 (3.3)*	*1.7 (1.4, 2.0)*	*79/3278 (2.4)*	*1.2 (1.0, 1.6)*
Non-fatal	*155/3286 (4.7)*	*2.4 (2.0, 2.8)*	*179/3278 (5.5)*	*2.8 (2.4, 3.3)*
MALE[b]	148/3286 (4.5)	2.3 (1.9, 2.7)	203/3278 (6.2)	3.2 (2.8, 3.7)
Other vascular event[c]	709/3286 (21.6)	11.0 (10.2, 11.9)	720/3278 (22.0)	11.4 (10.6, 12.2)
Non-vascular death	77/3286 (2.3)	1.2 (0.9, 1.5)	75/3278 (2.3)	1.2 (0.9, 1.5)
Second Event				
Any vascular	499/1012 (49.3)	49.5 (45.2, 54.0)	593/1102 (53.8)	62.0 (57.2, 67.2)
MACE	80/1012 (7.9)	7.9 (6.3, 9.9)	98/1102 (8.9)	10.3 (8.3, 12.5)
Fatal	48/1012 (4.7)	4.8 (3.5, 6.3)	51/1102 (4.6)	5.3 (4.0, 7.0)
Non-fatal	32/1012 (3.2)	3.2 (2.2, 4.5)	47/1102 (4.3)	4.9 (3.6, 6.5)
MALE	53/1012 (5.2)	5.3 (3.9, 6.9)	71/1102 (44.9)	7.4 (5.8, 9.4)
Other vascular event	366/1012 (36.2)	36.3 (32.7, 40.2)	424/1102 (38.5)	44.4 (40.2, 48.8)
Non-vascular death	30/1012 (3.0)	3.0 (2.0, 4.2)	25/1102 (2.3)	2.6 (1.7, 3.9)
Third Event				
Any vascular	249/451 (55.2)	76.9 (67.6, 87.0)	293/542 (54.1)	71.4 (63.5, 80.1)
MACE	34/451 (7.5)	10.5 (7.3, 14.7)	36/542 (6.6)	8.8 (6.1, 12.2)

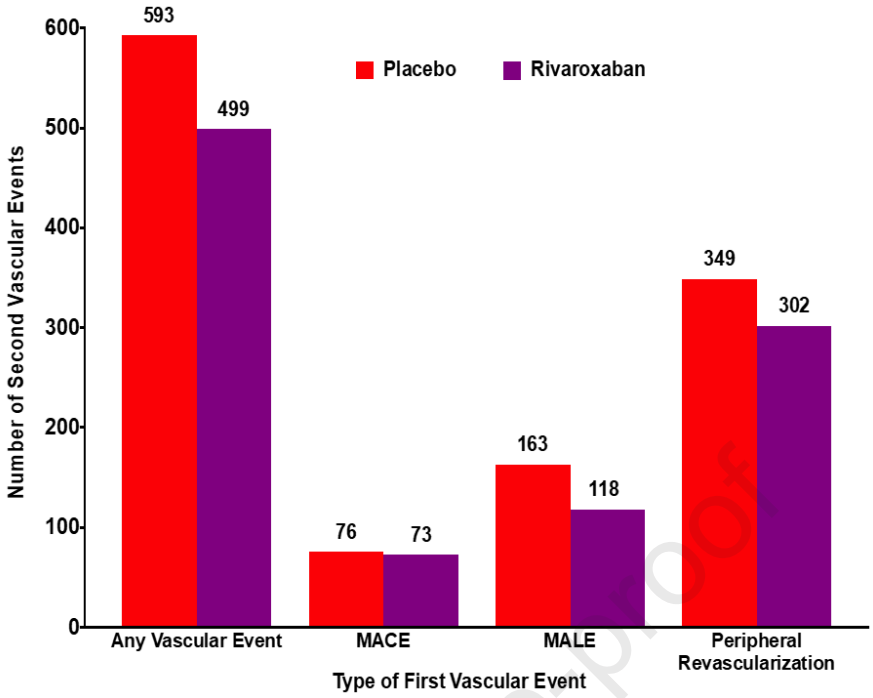
Fatal	17/451 (3.8)	5.2 (3.1, 8.4)	19/542 (3.5)	4.6 (2.8, 7.2)
Non-fatal	17/451 (3.8)	5.2 (3.1, 8.4)	17/542 (3.1)	4.1 (2.4, 6.6)
MALE	51/451 (11.3)	15.7 (11.7, 20.7)	58/542 (10.7)	14.1 (10.7, 18.3)
Other vascular event	164/451 (36.4)	50.6 (43.2, 59.0)	199/542 (36.7)	48.5 (42.0, 55.7)
Non-vascular death	5/451 (1.1)	1.5 (0.5, 3.6)	15/542 (2.8)	3.7 (2.0, 6.0)
Fourth and Subsequent Events				
Any vascular	318		461	
MACE	49		38	
Fatal	26		25	
Non-fatal	23		13	
MALE	67		107	
Other vascular event[c]	202		316	
Non-vascular death	10		8	
Total Events				
Any vascular	2186		2528	
MACE	426		430	
Fatal	199		174	
Non-fatal	227		256	
MALE	319		439	
Other vascular event[c]	1441		1659	
Non-vascular death	122		123	

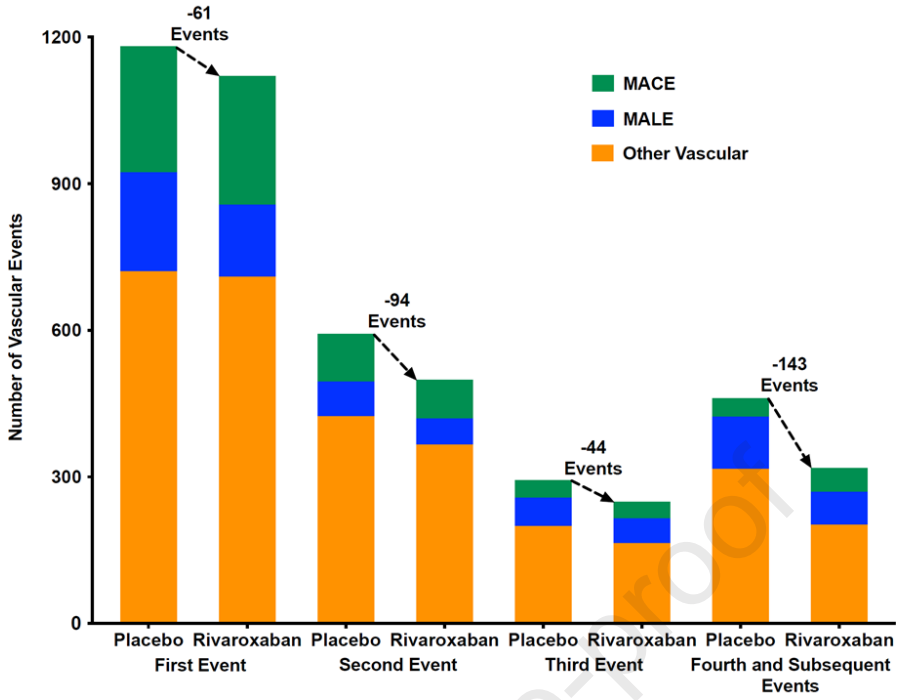
The denominator for second event reflects the number of patients with a non-fatal first event. The denominator for third event reflects the number of patients with a non-fatal second event. CI, confidence interval; p-y, patient-years.

[a] Major adverse cardiovascular event: non-fatal MI, non-fatal ischemic stroke, or vascular death

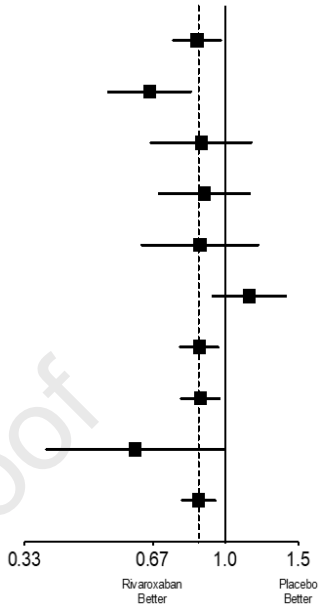
[b] Major adverse limb event: acute limb ischemia or major amputation for vascular causes

[c] Peripheral revascularization or venous thromboembolic event

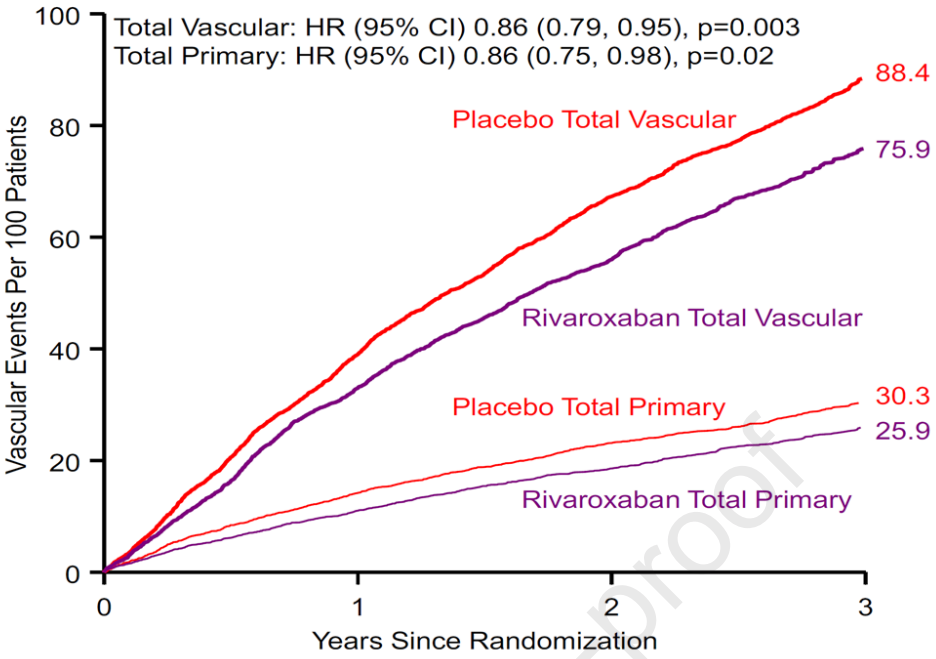




	Total Events per 100 Patients*		
	Rivaroxaban (n=3286)	Placebo (n=3278)	HR (95% CI)
Primary endpoint events	**25.9**	**30.3**	**0.86 (0.75, 0.98)**
Acute limb ischemia	6.6	10.2	0.66 (0.52, 0.83)
Major amputation	3.8	4.3	0.88 (0.66, 1.16)
Non-fatal myocardial infarction	5.3	5.7	0.89 (0.69, 1.15)
Non-fatal ischemic stroke	2.6	3.0	0.87 (0.63, 1.20)
Vascular death	7.1	6.5	1.14 (0.93, 1.40)
Other vascular events	**48.5**	**56.5**	**0.87 (0.78, 0.97)**
Peripheral revascularization	47.8	55.0	0.87 (0.78, 0.97)
Venous thromboembolic event	0.7	1.5	0.61 (0.37, 1.00)
All vascular events	**75.9**	**88.4**	**0.86 (0.79, 0.95)**



* 3 years after randomization



Online Table 1. Baseline Characteristics of Participants by Category of Number of Vascular Events

	(A) No Events (n=4263)	**(B) One Event (n=1209)**	**(C) Multiple Events (n=1092)**	**p-value**	
				(A) vs. (B) + (C)	**(B) vs. (C)**
Age, years, median (IQR)	67 (61, 73)	67 (61, 73)	67 (61, 73)	n.s.	n.s.
Female sex, %	25.6	25.5	27.8	n.s.	n.s.
BMI, kg/m^2, median (IQR)	26 (23, 29)	26 (23, 29)	26 (23, 29)	0.04	n.s.
White race, %	82.7	77.4	77.1	<0.0001	n.s.
Geographic region				<0.0001	0.01
North America, %	14.7	12.2	17.4		
Western Europe, %	31.2	31.8	30.4		
Eastern Europe, %	30.7	31.9	29.3		
Asia Pacific, %	16.1	16.6	15.6		
South America, %	7.3	7.4	7.3		
Risk factors and comorbidities					
Current smoker, %	34.5	35.4	35.0	n.s.	n.s.
Hypertension, %	80.2	83.1	84.1	0.0008	n.s.
Hyperlipidemia, %	57.8	63.9	64.5	<0.0001	n.s.
Coronary artery disease, %	29.3	35.2	35.9	<0.0001	n.s.

Heart failure, %	8.4	8.1	7.8	n.s.	n.s.
Carotid artery disease, %	8.2	9.2	10.6	0.02	n.s.
Diabetes mellitus, %	37.3	45.2	45.2	<0.0001	n.s.
Chronic kidney disease, %	8.3	10.8	11.0	0.0007	n.s.
eGFR<60 ml/min/1.73m^2, %	19.2	22.2	21.8	0.008	n.s.
SBP, mmHg, median (IQR)	135 (125, 145)	135 (125, 145)	135 (125, 146)	n.s.	n.s.
PAD history					
Index ABI ≤50, %	39.9	40.4	42.1	n.s.	n.s.
Prior revascularization, %	30.2	40.8	50.7	<0.0001	<0.0001
Prior amputation, %	5.0	8.0	7.4	<0.0001	n.s.
Qualifying revascularization					
Revascularization approach				0.0007	n.s.
Endovascular, %	65.3	68.4	70.5		
Surgical, %	34.7	31.6	29.5		
Randomization Strata				0.002	n.s.
Endovascular with clopidogrel, %	45.9	47.6	50.0		
Endovascular without clopidogrel, %	17.9	19.4	19.6		
Surgery, %	36.1	33.0	30.4		
Indication for revascularization				0.004	n.s.
Claudication, %	77.8	75.1	74.0		

Critical limb ischemia, %	22.2	24.9	26.0		
Long (≥15 cm) target lesion length, %	30.8	36.3	45.9	<0.0001	<0.0001
Atherectomy, %	3.4	5.5	9.2	<0.0001	0.0007
Thrombolysis, %	0.7	0.7	0.8	n.s.	n.s.
Medications					
Statin, %	78.7	82.4	82.2	0.0005	n.s.
Clopidogrel, %	49.5	51.0	53.7	0.03	n.s.
Randomized to rivaroxaban, %	50.8	51.4	45.7	n.s.	0.007

Values are median (quartile 1, quartile 3) or column percentages. n.s.: p>0.05, IQR = intraquartile range