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ORIGINAL RESEARCH

Sex-Based Differences in Outcomes Following Peripheral Artery Revascularization: Insights From VOYAGER PAD

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BACKGROUND: Despite high female prevalence of peripheral artery disease (PAD), little is known about sex-based outcomes after lower extremity revascularization (LER) for symptomatic PAD. The effects of rivaroxaban according to sex following LER have not been fully reported.

METHODS AND RESULTS: In VOYAGER PAD (Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease), low-dose rivaroxaban versus placebo on a background of aspirin reduced the composite primary efficacy outcome of cardiovascular and limb events in patients with PAD undergoing LER. Unplanned index limb revascularization was prespecified and prospectively ascertained. The primary safety outcome was Thrombolysis in Myocardial Infarction major bleeding. Analyses of outcomes and treatment effects by sex were performed using Cox proportional hazards models. Among 6564 randomly assigned patients followed for a median of 28 months, 1704 (26.0%) were women. Among patients administered placebo, women were at similar risk for the primary efficacy outcome (hazard ratio [HR], 0.90; [95% CI, 0.74–1.09]; *P*=0.29) as men, while female sex was associated with a trend toward higher risk of unplanned index limb revascularization (HR, 1.18; [95% CI, 1.00–1.40]; *P*=0.0499). Irrespective of sex, effects of rivaroxaban were consistent for the primary efficacy outcome (*P*-interaction=0.22), unplanned index limb revascularization (*P*-interaction=0.64), and bleeding (*P*-interaction=0.61). Women were more likely than men to discontinue study treatment (HR, 1.13; [95% CI, 1.03–1.25]; *P*=0.0099).

CONCLUSIONS: Among >1700 women with PAD undergoing LER, women and men were at similar risk for the primary outcome, but a trend for greater risk of unplanned index limb revascularization among women was observed. Effects of rivaroxaban were consistent by sex, though women more often discontinued treatment. Better understanding of sex-based outcomes and treatment adherence following LER is needed.

REGISTRATION: URL: http://clinicaltrials.gov; Unique identifier: NCT02504216.

Key Words: outcomes ■ peripheral artery disease ■ revascularization ■ sex

Peripheral artery disease (PAD) affects more than 200 million people worldwide and has been associated with equal or greater morbidity and mortality than coronary artery and cerebrovascular disease.[1–3] Patients with PAD are at heightened risk for major adverse cardiovascular events and major adverse limb events.[3] However, the dominant morbidity in PAD is related to limb outcomes, including need for

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with peripheral artery disease, women present with more severe disease, are more often treated with endovascular than surgical lower extremity revascularization, and may have greater risk for repeat unplanned index limb revascularization than men.
- The efficacy and safety of rivaroxaban compared with placebo on top of aspirin are consistent in women and men, though women discontinue treatment more often and for reasons unrelated to bleeding.

What Are the Clinical Implications?

- Greater awareness among providers of risk for peripheral artery disease and events after peripheral revascularization among women is important.
- More intensive antithrombotic therapy with low-dose rivaroxaban and aspirin after lower extremity revascularization for symptomatic peripheral artery disease can be considered to reduce postprocedure ischemic events in women at low risk for bleeding.
- Further investigation into the potential of reduced procedural patency and greater treatment discontinuation in women with peripheral artery disease after lower extremity revascularization is warranted.

Nonstandard Abbreviations and Acronyms

LER	lower extremity revascularization
UILR	unplanned index limb revascularization
VOYAGER PAD	Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease

lower extremity revascularization (LER).[4,5] The prevalence of PAD increases with age, and women are affected by PAD at least as often as men.[6]

Understanding sex-based differences in atherosclerotic cardiovascular diseases, including PAD, is important for optimizing patient outcomes. Studies of patients with coronary artery disease and cerebrovascular disease have demonstrated differences in treatments between women and men and suggest that ischemic and bleeding outcomes may differ on the basis of sex.[7–9] In patients with PAD, prior sex-based analyses of outcomes after LER have reported mixed results.[10–12] Therefore, the risk profile and outcomes among women undergoing LER for symptomatic PAD are not well understood. Beyond outcomes, sex-based differences in participation in large cardiovascular trials have also been observed and warrant additional investigation.[13]

VOYAGER PAD (Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) randomly assigned patients with symptomatic PAD undergoing LER to rivaroxaban 2.5 mg twice daily versus placebo on a background of low-dose aspirin and showed significant reductions in severe limb and cardiovascular events with rivaroxaban.[14] VOYAGER PAD provides a unique opportunity to better understand sex-based differences in patient characteristics, clinical outcomes, and trial metrics in a study of patients with PAD managed with LER. In addition, the efficacy and safety of rivaroxaban have not been fully reported by sex in this population.

METHODS

Data Source

Data were from VOYAGER PAD (NCT02504216), the primary results of which have been previously published.[14] The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results. In VOYAGER PAD, patients were randomly assigned to rivaroxaban 2.5 mg twice daily versus placebo after LER for symptomatic PAD and treated with aspirin 100 mg daily. Clopidogrel was allowed for up to 6 months per the investigator's discretion. The trial protocol was designed and overseen by Colorado Prevention Center Clinical Research (an academic research organization affiliated with the University of Colorado), the academic executive committee, and the sponsors, Bayer and Janssen Pharmaceuticals. Colorado Prevention Center Clinical Research holds the clinical database and independently performed all analyses for this publication. VOYAGER PAD was conducted in accordance with the principles of the Declaration of Helsinki; all patients provided written, informed consent, and institutional review boards at participating institutions approved the protocols.

Study Population

Eligible patients were ≥50 years old, had an abnormal ankle-brachial index or toe-brachial index and imaging evidence of PAD distal to the external iliac artery, and underwent successful infrainguinal LER for claudication or critical limb ischemia via an endovascular

(including hybrid) or surgical approach within the previous 10 days. Key exclusion criteria included planned use of dual antiplatelet therapy for >6 months; a medical indication for systemic anticoagulation; recent acute limb ischemia or acute coronary syndrome; increased risk of bleeding; significantly reduced renal function; and prior intracranial hemorrhage, stroke, or transient ischemic attack.

Outcomes

The primary efficacy outcome for VOYAGER PAD was a composite of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death. Secondary outcomes as specified in the primary manuscript included individual components of the primary outcome, unplanned index limb revascularization (UILR), which was prospectively ascertained, and hospitalization for coronary or peripheral event of a thrombotic nature.[14] Additional prespecified categories of vascular events recorded in the trial included subsequent peripheral revascularizations of both the index and contralateral leg and venous thromboembolic events. Nonvascular deaths were recorded during follow-up. The primary safety outcome was Thrombolysis in Myocardial Infarction major bleeding. Secondary safety outcomes included bleeding according to International Society of Thrombosis and Hemostasis and Bleeding Academic Research Consortium scales. An independent clinical events committee blinded to treatment assignment adjudicated all deaths; potential ischemic cardiac, cerebrovascular, and vascular limb events; and bleeding events.

Statistical Analysis

Patient sex was a prespecified subgroup analysis. Categorical variables are reported as number (percentage), and continuous variables reported as median (quartile 1–quartile 3). Comparisons of baseline characteristics grouped by sex were by Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Associations of sex with outcomes within the placebo group were examined with Cox regression models stratified by the index revascularization approach (endovascular versus surgical), summarized by hazard ratios (HRs) with associated Wald 95% CIs and log-rank *P* values. Unadjusted models were employed given the objective of identifying observed sex-based differences in outcomes. However, the hazard of UILR was observed to be significantly different between sexes and, given sex-based biologic plausibility for differences in this outcome, it was further assessed with a Cox model adjusted for age, body mass index, hypertension, hyperlipidemia, diabetes, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, current smoking, and endovascular versus surgical revascularization. Covariates were selected on the basis of clinical judgment. A formal backward selection process was not used. The treatment effects of rivaroxaban versus placebo on time to first events were assessed by Cox proportional hazards model, stratified by index revascularization approach, with terms for treatment, sex, and their interaction, and summarized by HRs with associated Wald 95% CIs and *P* values for the interaction terms. Analyses of ischemic outcomes were primarily performed according to the intention-to-treat principle, including all patients and events from randomization to the study efficacy cutoff date. Ischemic outcomes, as well as bleeding, were additionally evaluated using prespecified on-treatment analyses including all patients and events from randomization until 2 days following permanent discontinuation of the study drug according to actual treatment received. Additional analyses included intention-to-treat of total vascular events including total occurrences of the primary composite plus any subsequent peripheral revascularization and venous thromboembolic events. Total events were analyzed by a marginal proportional hazards model that allows for the possibility of multiple vascular events within a given participant while treating nonvascular death as a competing terminal event. A robust sandwich variance estimate for the estimated standard error of the log HR was used to account for the dependence of event times within individual patients. *P* values <0.05, 2-tailed, were considered statistically significant, with no adjustment for multiple testing. Analyses were performed in SAS 9.4 and S+ 8.2.

RESULTS

Baseline Patient Characteristics

Among 6564 patients randomized in VOYAGER PAD and followed for a median of 28 months (interquartile range, 22–34), 26.0% (n=1704) were women. Baseline characteristics according to sex are shown in Table 1. Compared with men, women had a greater prevalence of risk factors, including older age, hypertension, hyperlipidemia, and renal insufficiency; in contrast, men had more prevalent diagnosed coronary artery disease and were more often current smokers. Baseline use of clopidogrel was greater among women than men.

Compared with men, women presented with more severe PAD (Rutherford 4–6, 26.0% versus 22.8%; *P*=0.0105) and more often underwent LER for critical limb ischemia. Women were more frequently treated with endovascular LER (73.7% versus 64.3%; *P*<0.0001) than men. Among patients treated with endovascular LER, use of atherectomy was more common in women than men, and in both sexes,

Table 1. Baseline Characteristics According to Sex

Characteristic	Female (N=1704)	Male (N=4860)	*P* value
Age, y	69 (63–76)	66 (60–72)	<0.0001
Body mass index, kg/m^2	25.8 (22.9–29.3)	26.0 (23.5–29.0)	0.0524
White race	1366 (80.2)	3937 (81.0)	0.45
Geographic region			<0.0001
North America	229 (13.4)	465 (9.6)	
Western Europe	461 (27.1)	1365 (28.1)	
Eastern Europe	610 (35.8)	1989 (40.9)	
Asia Pacific	235 (13.8)	726 (14.9)	
Latin America	169 (9.9)	315 (6.5)	
Risk factors and comorbidities			
Current smoker	447 (26.2)	1832 (37.7)	<0.0001
Hypertension	1470 (86.3)	3872 (79.7)	<0.0001
Hyperlipidemia	1072 (62.9)	2867 (59.0)	0.0045
Coronary artery disease	462 (27.1)	1605 (33.0)	<0.0001
Heart failure	124 (7.3)	415 (8.5)	0.11
Carotid artery disease	152 (8.9)	423 (8.7)	0.80
Diabetes	711 (41.7)	1918 (39.5)	0.10
eGFR <60 mL/min per 1.73 m^2	502 (29.5)	825 (17.0)	<0.0001
PAD history			
Index ankle-brachial index ≤0.50	681 (40.0)	1971 (40.6)	0.69
Prior revascularization	594 (34.9)	1742 (35.8)	0.48
Prior amputation	89 (5.2)	301 (6.2)	0.15
Qualifying revascularization			
Revascularization approach			<0.0001
Endovascular	1256 (73.7)	3123 (64.3)	
Surgical	448 (26.3)	1737 (35.7)	
Indication for revascularization			0.0057
Claudication	1264 (74.2)	3767 (77.5)	
Critical limb ischemia	440 (25.8)	1093 (22.5)	
Location (endovascular)*			0.19
Popliteal or above	1261 (89.3)	3322 (90.6)	
Infra-popliteal	139 (9.8)	305 (8.3)	
Other	12 (0.8)	39 (1.1)	
Location (surgical bypass)†			0.61
Above-knee popliteal	180 (61.6)	736 (61.6)	
Below-knee popliteal	88 (30.1)	339 (28.4)	
Tibial/Pedal	24 (8.2)	119 (10.0)	
Long (≥15 cm) target lesion length	558 (32.7)	1694 (34.9)	0.12
Atherectomy*	114 (9.1)	197 (6.3)	0.0017
Drug-coated device*	385 (30.6)	973 (31.2)	0.77
Medications			
Statin	1362 (79.9)	3887 (80.0)	0.97
Clopidogrel	932 (54.7)	2381 (49.0)	<0.0001

Numbers in table are n (%) or median (quartile 1–quartile 3). eGFR indicates estimated glomerular filtration rate; and PAD, peripheral artery disease.

*Percentages calculated among patients undergoing endovascular revascularization.

†Percentages calculated among patients undergoing surgical revascularization.

use of drug-coated devices was similar, and treatment of disease at the level of the popliteal artery or above was more common than infrapopliteal disease. Patients undergoing surgical LER with bypass had predominantly above-knee popliteal targets, irrespective of sex.

Outcomes in Women Versus Men Assigned to Placebo

Outcomes were examined according to sex in the placebo group. Women and men were at similar risk for the primary composite outcome (17.9% versus 20.6% at 3 years; HR, 0.90; [95% CI, 0.74–1.09]; *P*=0.29; Figure 1A), regardless of the indication for revascularization (claudication versus critical limb ischemia, *P*-interaction=0.8661). Similar risk in the overall population according to sex was also observed for prespecified secondary outcomes, including individual components of the primary outcome, hospitalization for thrombotic events, all-cause mortality, and venous thromboembolism (Table S1). In contrast, female sex was associated with a trend for higher risk of UILR during follow-up than male sex (25.3% versus 21.5% at 3 years; HR, 1.18; [95% CI, 1.00–1.40]; *P*=0.0499; Figure 1B). Even after adjustment for key comorbidities, this association persisted (adjusted HR, 1.23; [95% CI, 1.04–1.46]; *P*=0.0179). This relationship, which was also observed among patients randomly assigned to rivaroxaban (Figure S1), was not modified by initial index revascularization approach (*P*-interaction=0.98), with women administered placebo at similarly elevated risk for UILR for endovascular (HR, 1.18; [95% CI, 0.98–1.43]) and surgical (HR, 1.19; [95% CI, 0.83–1.70]) procedures in the intention-to-treat analysis of events. In contrast, a trend for greater relative risk of UILR in women versus men assigned to placebo was observed for patients undergoing revascularization for claudication (HR, 1.26; [95% CI, 1.04–1.53]) but not critical limb ischemia (HR, 0.94; [95% CI, 0.67–1.32]; *P*-interaction=0.14).

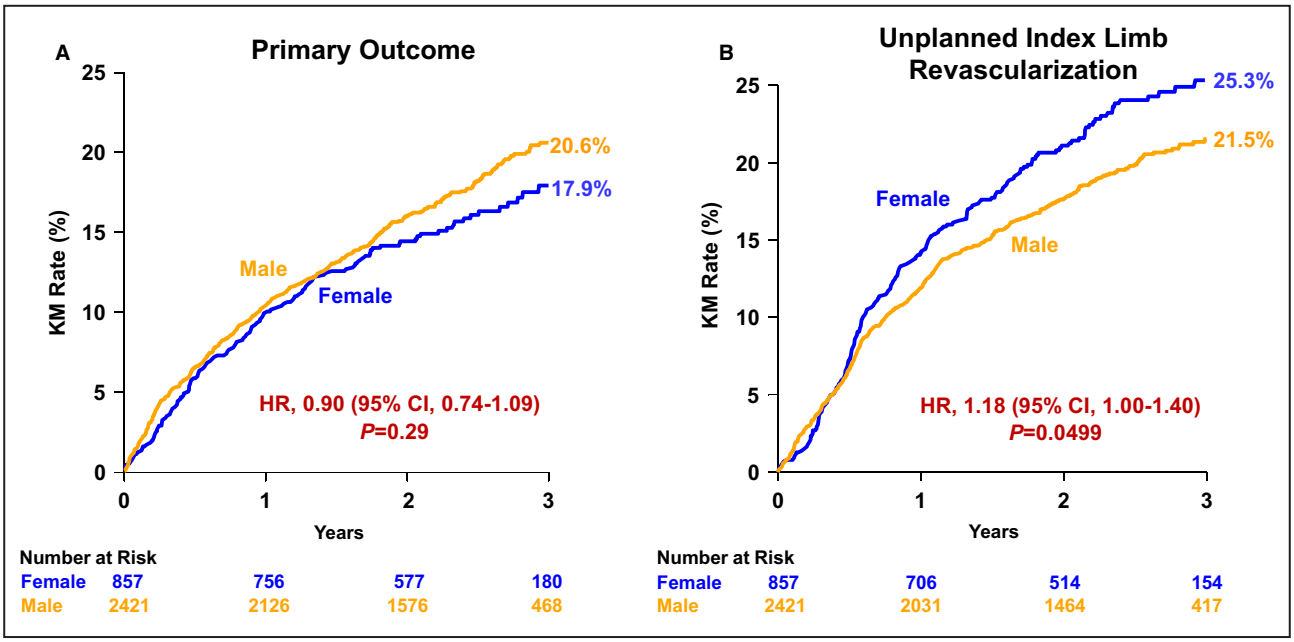

Figure 1. Primary composite outcome and unplanned index limb revascularization in placebo patients.
Shown are Kaplan-Meier curves for the primary outcome (**A**) and unplanned index limb revascularization (**B**) by sex among patients administered placebo. Hazard ratios (HR) reflect stratification for endovascular or surgical revascularization.

Effects of Rivaroxaban in Women Versus Men

The efficacy and safety of rivaroxaban versus placebo were examined according to sex (Figure 2; Tables S2 and S3). In the overall population analyzed as intention-to-treat, rivaroxaban significantly reduced risk of the primary outcome compared with placebo (HR, 0.85; [95% CI, 0.76–0.96]; Figure 2). Although the

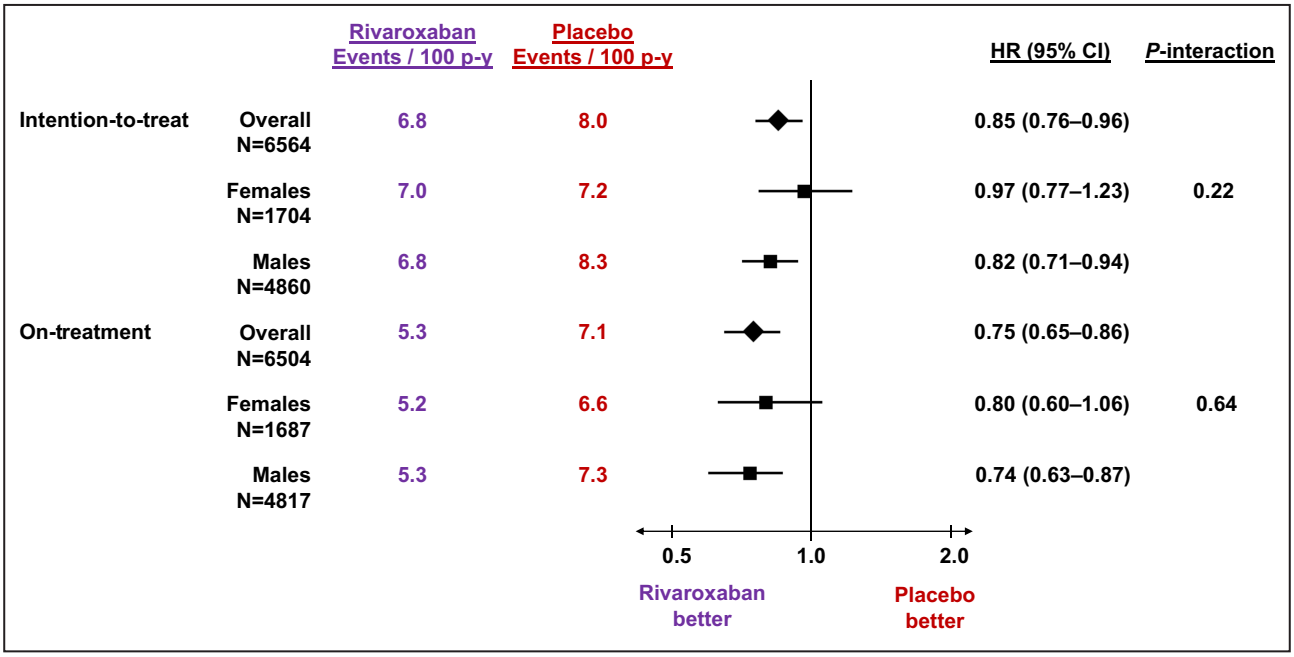

Figure 2. Effects of rivaroxaban compared to placebo for the primary outcome by sex.
Shown are event rates, HR, and 95% CI for the primary composite outcome by sex in intention-to-treat and on-treatment analyses. Analyses performed according to the intention-to-treat principle included all patients and events from randomization to the study efficacy cutoff date according to randomized treatment assignment. On-treatment analyses included all patients and events from randomization until 2 days following permanent discontinuation of the study drug according to actual treatment received. Hazard ratios (HR) reflect stratification for endovascular or surgical revascularization. p-y indicates patient-years.

benefit was consistent among women and men (*P*-interaction=0.22), the relative benefit of rivaroxaban on the primary outcome was numerically lower for women (HR, 0.97; [95% CI, 0.77–1.23]) than for males (HR, 0.82; [95% CI, 0.71–0.94]). In VOYAGER PAD, women prematurely discontinued treatment more often than men (observed incidences of treatment discontinuation in 36.1% and 33.6% of women receiving at least 1 dose of rivaroxaban and placebo, respectively, versus 32.1% and 30.2% of men; across treatment groups, women versus men HR, 1.13; [95% CI, 1.03–1.25]; *P*=0.0099; Figure 3). As shown in Table S4, approximately half of premature discontinuations were related to adverse events among all patients, while patient decision was a greater driver of treatment discontinuation for women than men (28.1% versus 23.0%; *P*=0.0174). Given greater treatment discontinuation observed among women, an on-treatment analysis of the effect of rivaroxaban was performed (Figure 2). When analyzed on-treatment, the point estimate for effect of rivaroxaban among women was lower (HR, 0.80; [95% CI, 0.60–1.06]), with relative benefits of rivaroxaban consistent for women and men (HR, 0.74; [95% CI, 0.63–0.87]; *P*-interaction=0.64).

In the overall population, rivaroxaban significantly reduced UILR (HR, 0.88; [95% CI, 0.79–0.99]). The benefit of rivaroxaban on UILR was similar for women and men when analyzed as intention-to-treat (*P*-interaction=0.64). In terms of total vascular events, the relative benefits of rivaroxaban versus placebo were also similar for women (29.7% versus 33.5%; HR, 0.88; [95% CI, 0.73–1.06]) and men (26.2% versus 30.5%; HR, 0.86; [95% CI, 0.77–0.96]; *P*-interaction=0.81). The numerical excess in the principal safety outcome of Thrombolysis in Myocardial Infarction major bleeding (*P*-interaction=0.61) and other measures of bleeding with rivaroxaban was similar for women and men (Table S3).

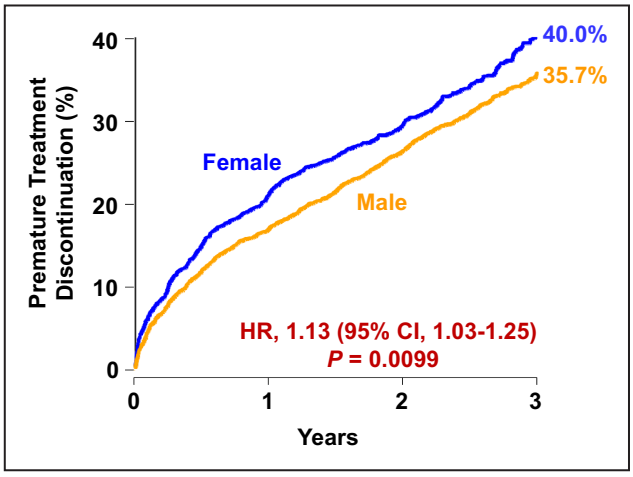

Figure 3. Study treatment discontinuation by sex.
Cumulative incidences of premature study treatment discontinuation are shown for women and men. HR indicates hazard ratio.

Enrollment and Medication Adherence According to Sex of Site Investigator

In VOYAGER PAD, a total of 6564 patients were randomized at 542 sites in 34 countries. Of 514 sites where the sex of the site investigator could be determined retrospectively, 69 (13.4%) were women and 445 (86.6%) were men. The percentage of female participants enrolled was similar at sites where the site investigator was a woman (median, 25.0%; IQR, 14.3%–33.3%) or man (median, 25.0%; IQR, 9.1%–38.1%; *P*=0.89). Total participant enrollment, however, was higher at sites where the site investigator was a woman (median, 10 patients; IQR, 7–17) than at sites where the site investigator was male (median, 8 patients; IQR, 4–14; *P*=0.0230). Additionally, premature treatment discontinuation was lower at sites with female investigators than at sites with male investigators (29.4% versus 32.7%; *P*=0.0375).

DISCUSSION

This analysis from VOYAGER PAD including more than 1700 women is one of the largest trial experiences of women undergoing LER for symptomatic PAD. However, only a quarter of the study population were women. Compared with men, women had more atherosclerotic risk factors, with the exception of less current smoking, and they presented with more severe PAD and were more often treated with endovascular LER and atherectomy. Despite similar risk for the primary outcome among patients administered placebo, there was a trend for greater risk for UILR among women than men, even after adjustment for key comorbidities and irrespective of revascularization approach. Treatment effects for rivaroxaban with regard to efficacy and safety were overall consistent between sexes. However, greater treatment discontinuation was observed among women than men, and women more often discontinued treatment because of patient decisions. These results are hypothesis generating and illustrate the need for efforts to better understand factors contributing to sex-based differences in outcomes after LER and clinical trial participation and treatment adherence.

This analysis demonstrates important sex-based differences in clinical presentation among patients with PAD undergoing LER. Although women had a higher risk profile with respect to risk factors for atherosclerosis, except for less smoking, women were less likely to have documented coronary artery disease than men. Despite this, women more commonly presented with more advanced PAD. These observations support the

notion that PAD and coronary disease are different and may reflect both biological differences as well as contributions of patient and provider factors resulting in delayed diagnosis of PAD. In addition, prior studies have reported that women are more likely than men to have atypical leg symptoms or to be asymptomatic, though many patients without leg symptoms are often found to have unrecognized functional decline.[15] Overall awareness of PAD also remains low, resulting in underdiagnosis and undertreatment of disease.

Differences in LER treatment according to sex were also observed. Despite similar target lesion length, women more often underwent endovascular versus surgical LER than men. This may reflect greater procedural risk related to older age and comorbidities or lower likelihood of adequate size of venous conduit or target vessel among women and also likely explains the more frequent baseline use of clopidogrel among women. Within the endovascular subgroup, women were more likely to be treated with atherectomy, which may be related to greater severity of disease. Overall, these findings illustrate how patient risk profiles and anatomy may contribute to sex-based differences in treatment modality.

Beyond treatment differences, we observed sex-based variations in postprocedural outcomes, findings that are hypothesis generating. Prior studies have reported conflicting results regarding clinical outcomes among women and men undergoing LER but have been limited by small sample size, single-center data, use of administrative data, and lack of adjudicated outcomes.[10–12] In VOYAGER PAD, a large, international population with prospectively collected and adjudicated outcomes, risk for the primary composite outcome was similar for women and men. However, women were at ≈20% greater risk for UILR than men, despite greater clopidogrel use, less current smoking, which has been associated with reduced patency after LER,[16] and similar use of drug-coated devices, which have been shown to improve patency of endovascular LER.[17] More severe disease and smaller vessel size in women,[18] resulting in greater technical difficulty, may be contributing factors. Sex-based variation in endothelial responses to vascular stressors have also been observed.[19] Importantly, evidence for the efficacy of LER in PAD has been derived mainly from men, with women accounting for approximately one-third of participants in randomized LER trials.[15] This paucity of data on device use in women may partly explain lower use in women and poorer outcomes when used. Furthermore, medical therapies are underused in women with atherosclerotic cardiovascular disease; even among treated patients, women are less likely than men to achieve target levels for blood pressure, cholesterol, and hemoglobin A1c.[20–22] Increased risk of repeat limb revascularization among women may thus reflect a combination of biology and bias and highlights the need for better understanding of LER techniques and devices and optimization of medical therapies. Beyond PAD, increasing recognition of the importance of sex-based differences in pathophysiology, treatment, and outcomes has led to recent suggestions for sex-specific cardiovascular guidelines.[23] The observed trend in increased relative risk of UILR among women versus men after revascularization for claudication but not critical limb ischemia may support consideration of sex and disease state in risk-benefit assessments of LER for PAD and warrants further investigation.

The efficacy and safety of rivaroxaban versus placebo was overall consistent in both sexes. Attenuation of benefit for rivaroxaban was observed among females in intention-to-treat but not on-treatment analyses, suggesting that this difference could be explained by the greater treatment discontinuation observed among women. Treatment discontinuation related to patient decision was more common among women; our analysis suggests that differential treatment discontinuation was not related to bleeding complications, which occurred at similar rates for both sexes even when assessed using more sensitive measures of bleeding. Lower female medication adherence has been observed in other conditions, including hypertension and hyperlipidemia.[24,25] Underestimation of cardiovascular risk in women by patients and providers, as previously demonstrated,[26,27] may play a role. Interestingly, we also observed that treatment adherence was greater at sites with female site investigators. Increased education regarding the importance of medication adherence and better understanding of treatment discontinuation among women are needed.

Finally, the modest proportion of female patients in VOYAGER PAD is noteworthy. Despite the high burden of PAD in women and the fact that this is one of the largest contemporary clinical trial experiences of LER for PAD, women comprised only approximately one-fourth of randomized patients. Women represent on average 46% (ranging from 22% to 81%) of participants in clinical trials supporting regulatory approval of cardiovascular drugs in the United States; however, female participation in trials of atherosclerotic cardiovascular disease, including PAD, continues to lag.[28] In VOYAGER PAD, underrepresentation of female participants was unrelated to sex of the site investigator, though female site investigators did better with overall enrollment than men. The lower participation of women in clinical trials in general is likely multifactorial and may reflect factors such as lower awareness of clinical trials, risk aversion, lack of economic resources, and a greater burden of caring for family members compared with men. Increased awareness of the importance of trial participation and creative solutions, such as flexible hours for study visits, remote or home-based visits,

and help with childcare and transportation, may help to improve participation of women in clinical trials.

Limitations of this analysis should be noted. The choice of medical and device-based therapies was based on physician's discretion. Operator practice patterns and patient characteristics of subjects participating in VOYAGER PAD may be different than those in nonclinical trial settings, potentially limiting the generalizability of these results. VOYAGER PAD was not powered to show sex-specific differences, and randomization was not stratified by sex.

CONCLUSIONS

In this analysis of >1700 women undergoing LER for symptomatic PAD in VOYAGER PAD, women made up approximately one-fourth of the study population. Differences in clinical presentation, procedural treatments, and outcomes were observed between sexes. In particular, compared with men, female sex was associated with a trend toward higher risk for UILR during follow-up, even after adjustment for key comorbidities, though this finding should be considered hypothesis generating. The effects of rivaroxaban were consistent in both sexes, though women prematurely discontinued treatment more frequently. Further research to better understand sex-based differences in outcomes after LER, including lower procedural patency, and medication adherence is needed.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figure S1

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340. doi: 10.1016/S0140-6736(13)61249-0
2. Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, Olsen AM, Jones WS, Torp-Pedersen C, Fosbol EL. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. *Eur J Prev Cardiol*. 2015;22:317–325. doi: 10.1177/2047487313519344
3. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial. *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235
4. Bonaca MP, Scirica BM, Creager MA, Olin J, Bounameaux H, Dellborg M, Lamp JM, Murphy SA, Braunwald E, Morrow DA. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. *Circulation*. 2013;127:1522–1529, 1529.e1-6
5. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, 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;35:2864–2872. doi: 10.1093/eurheartj/ehu080
6. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14:156–170. doi: 10.1038/nrcardio.2016.179
7. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947. doi: 10.1161/CIR.0000000000000351
8. Liang Y, Zhu J, Liu L, Anand SS, Connolly SJ, Bosch J, Guzik TJ, O'Donnell M, Dagenais GR, Fox KA, et al. Efficacy and safety of

rivaroxaban plus aspirin in women and men with chronic coronary or peripheral artery disease. *Cardiovasc Res*. 2021;117:942–949. doi: 10.1093/cvr/cvaa100

9. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, Guerrero M, Kunadian V, Lam CSP, Maas A, et al. The lancet women and cardiovascular disease commission: reducing the global burden by 2030. *Lancet*. 2021;397:2385–2438. doi: 10.1016/S0140-6736(21)00684-X
10. Lee MS, Choi BG, Hollowed J, Han SK, Baek MJ, Gi Ryu Y, Choi SY, Byun JK, Mashaly A, Park Y, et al. Assessment of sex differences in 5-year clinical outcomes following endovascular revascularization for peripheral artery disease. *Cardiovasc Revasc Med*. 2020;21:110–115. doi: 10.1016/j.carrev.2019.03.018
11. Ramkumar N, Suckow BD, Brown JR, Sedrakyan A, Cronenwett JL, Goodney PP. Sex-based assessment of patient presentation, lesion characteristics, and treatment modalities in patients undergoing peripheral vascular intervention. *Circ Cardiovasc Interv*. 2018;11:e005749. doi: 10.1161/CIRCINTERVENTIONS.117.005749
12. Lo RC, Bensley RP, Dahlberg SE, Matyal R, Hamdan AD, Wyers M, Chaikof EL, Schermerhorn ML. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg*. 2014;59:409–418.e3. doi: 10.1016/j.jvs.2013.07.114
13. Lau ES, Braunwald E, Morrow DA, Giugliano RP, Antman EM, Gibson CM, Scirica BM, Bohula EA, Wiviott SD, Bhatt DL, et al. Sex, permanent drug discontinuation, and study retention in clinical trials: insights from the TIMI trials. *Circulation*. 2021;143:685–695. doi: 10.1161/CIRCULATIONAHA.120.052339
14. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004. doi: 10.1056/NEJMoa2000052
15. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, Hiatt WR, Karas RH, Lovell MB, McDermott MM, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1449–1472. doi: 10.1161/CIR.0b013e31824c39ba
16. Young JC, Paul NJ, Karatas TB, Kondrasov SA, McGinigle KL, Crowner JR, Pascarella L, Farber MA, Kibbe MR, Marston WA, et al. Cigarette smoking intensity informs outcomes after open revascularization for peripheral artery disease. *J Vasc Surg*. 2019;70:1973–1983.e5. doi: 10.1016/j.jvs.2019.02.066
17. Tepe G, Laird J, Schneider P, Brodmann M, Krishnan P, Micari A, Metzger C, Scheinert D, Zeller T, Cohen DJ, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131:495–502. doi: 10.1161/CIRCULATIONAHA.114.011004
18. Piazza M, Squizzato F, Bassini S, Chincarini C, Grego F, Antonello M. The impact of female sex on the outcomes of endovascular treatment for iliac lesions. *J Vasc Surg*. 2020;71:2039–2047. doi: 10.1016/j.jvs.2019.08.271
19. Pabon M, Cheng S, Altin SE, Sethi SS, Nelson MD, Moreau KL, Hamburg N, Hess CN. Sex differences in peripheral artery disease. *Circ Res*. 2022;130:496–511. doi: 10.1161/CIRCRESAHA.121.320702
20. McDermott MM, Greenland P, Reed G, Mazor KM, Merriam PA, Graff R, Tao H, Pagoto S, Manheim L, Kibbe MR, et al. Gender differences in cholesterol-lowering medication prescribing in peripheral artery disease. *Vasc Med*. 2011;16:428–435. doi: 10.1177/1358863X11425879
21. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care*. 2005;28:514–520. doi: 10.2337/diacare.28.3.514
22. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX Jr, Boden WE, Roe MT, Ohman EM, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005;45:832–837. doi: 10.1016/j.jacc.2004.11.055
23. DeFilippis EM, Van Spall HGC. Is it time for sex-specific guidelines for cardiovascular disease? *J Am Coll Cardiol*. 2021;78:189–192. doi: 10.1016/j.jacc.2021.05.012
24. Rea F, Mella M, Monzio Compagnoni M, Cantarutti A, Merlino L, Mancia G, Corrao G. Women discontinue antihypertensive drug therapy more than men. Evidence from an Italian population-based study. *J Hypertens*. 2020;38:142–149. doi: 10.1097/HJH.0000000000002222
25. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. *Am Heart J*. 2013;165:665–678,678.e1
26. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. *Circ Cardiovasc Qual Outcomes*. 2010;3:120–127. doi: 10.1161/CIRCOUTCOMES.109.915538
27. Wenger NK. Women and coronary heart disease: a century after Herrick: understudied, underdiagnosed, and undertreated. *Circulation*. 2012;126:604–611. doi: 10.1161/CIRCULATIONAHA.111.086892
28. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, Elahi M, Temple RJ, Woodcock J. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol*. 2018;71:1960–1969. doi: 10.1016/j.jacc.2018.02.070

Supplemental Material

Table S1. Outcomes According to Sex in Patients Randomized to Placebo.

	Events per 100 patient-years		
Endpoint	**Female (N= 857)**	**Male (N=2421)**	**Unadjusted HR (95% CI)**
Primary outcome: Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or Cardiovascular Death	7.2	8.3	0.90 (0.74-1.09)
Acute Limb Ischemia	2.8	3.1	1.01 (0.75-1.37)
Major Amputation for Vascular Causes	1.6	1.4	1.22 (0.81-1.84)
Non-fatal Myocardial Infarction	1.9	1.9	0.96 (0.67-1.39)
Non-fatal Ischemic Stroke	0.9	1.1	0.80 (0.47-1.34)
Cardiovascular Death	2.2	2.2	1.06 (0.76-1.49)
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or Coronary Heart Disease Death	6.7	7.4	0.95 (0.78-1.16)
Unplanned Index Limb Revascularization	11.0	9.1	1.18 (1.00-1.40)
Hospitalization for Thrombotic Coronary or Peripheral Event	4.9	4.8	1.06 (0.84-1.34)
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or All-Cause Death	8.2	9.7	0.87 (0.73-1.04)
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic or Hemorrhagic Stroke, or Cardiovascular Death	7.2	8.4	0.90 (0.75-1.09)
All-Cause Death	3.3	3.8	0.91 (0.70-1.19)
Venous Thromboembolism	0.4	0.6	0.70 (0.32-1.53)

Table S2. Efficacy of Rivaroxaban Compared with Placebo by Sex.

	Events per 100 patient-years			
Endpoint	**Rivaroxaban (N=3256)**	**Placebo (N=3248)**	**HR (95% CI)**	**$P_{interaction}$**
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or Cardiovascular Death				0.22
Female	7.0	7.2	0.97 (0.77-1.23)	
Male	6.8	8.3	0.82 (071-0.94)	
Acute Limb Ischemia				0.76
Female	2.0	2.8	0.71 (0.48-1.07)	
Male	2.0	3.1	0.66 (0.52-0.84)	
Major Amputation for Vascular Causes				0.71
Female	1.3	1.6	0.83 (0.49-1.38)	
Male	1.3	1.4	0.93 (0.68-1.26)	
Non-fatal Myocardial Infarction				0.71
Female	1.5	1.9	0.82 (0.51-1.31)	
Male	1.7	1.9	0.91 (0.69-1.19)	
Non-fatal Ischemic Stroke				0.17
Female	1.1	0.9	1.26 (0.68-2.36)	
Male	0.9	1.1	0.76 (0.52-1.10)	
Cardiovascular Death				0.34
Female	2.9	2.2	1.35 (0.92-1.98)	
Male	2.3	2.2	1.08 (0.85-1.37)	
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or Coronary Heart Disease Death				0.54
Female	5.8	6.7	0.86 (0.67-1.11)	
Male	5.8	7.4	0.79 (0.68-0.91)	
Unplanned Index Limb Revascularization				0.64
Female	10.1	11.0	0.92 (0.75-1.13)	

Male	7.8	9.1	0.87 (0.76-0.99)	
Hospitalization for Thrombotic Coronary or Peripheral Event				0.84
Female	3.4	4.9	0.71 (0.52-0.96)	
Male	3.5	4.8	0.73 (0.61-0.88)	
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Non-fatal Ischemic Stroke, or All-Cause Death				0.21
Female	8.2	8.2	1.00 (0.80-1.25)	
Male	8.2	9.7	0.85 (0.75-0.97)	
Acute Limb Ischemia, Major Amputation for Vascular Causes, Non-fatal Myocardial Infarction, Ischemic Stroke, or Cardiovascular Death				0.20
Female	7.1	7.2	0.98 (0.77-1.24)	
Male	6.8	8.4	0.82 (0.72-0.94)	
All-Cause Death				0.24
Female	4.2	3.3	1.28 (0.93-1.74)	
Male	3.9	3.8	1.02 (0.85-1.23)	
Venous Thromboembolism				0.23
Female	0.4	0.4	1.02 (0.38-2.72)	
Male	0.3	0.6	0.51 (0.28-0.92)	

Table S3. Safety of Rivaroxaban Compared with Placebo by Sex.

	Events per 100 patient-years			
Endpoint	**Rivaroxaban (N=3256)**	**Placebo (N=3248)**	**HR (95% CI)**	**$P_{interaction}$**
TIMI major bleeding				0.61
Female	0.9	0.5	1.73 (0.76-3.95)	
Male	1.0	0.7	1.35 (0.87-2.09)	
Intracranial hemorrhage				0.69
Female	0.2	0.2	1.04 (0.21-5.14)	
Male	0.2	0.3	0.72 (0.32-1.61)	
Fatal bleeding				n/a
Female	0	0	n/a	
Male	0.1	0.1	1.01 (0.33-3.14)	
Intracranial or fatal bleeding				0.85
Female	0.2	0.2	1.04 (0.21-5.15)	
Male	0.3	0.3	0.88 (0.43-1.80)	
ISTH major bleeding				0.88
Female	2.3	1.7	1.38 (0.84-2.25)	
Male	2.1	1.5	1.44 (1.07-1.95)	
BARC major bleeding				0.77
Female	1.4	1.0	1.41 (0.75-2.63)	
Male	1.4	1.1	1.26 (0.89-1.79)	

BARC, Bleeding Academic Research Consortium; ISTH, International Society of Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction

Table S4. Reasons for Premature Discontinuation of Study Treatment.

Reason for Premature Discontinuation	Female (N=588)	Male (N=1,503)
Due to adverse event	294 (50.0)	788 (52.4)
Patient decision	165 (28.1)	346 (23.0)
Physician decision	15 (2.6)	35 (2.3)
Protocol criteria	54 (9.2)	172 (11.4)
Administrative	39 (6.6)	105 (7.0)
Other	21 (3.6)	57 (3.8)

Numbers in table are n (%)

Figure S1. Unplanned Index Limb Revascularization in Rivaroxaban Patients. Shown are Kaplan-Meier curves for the UILR by sex among patients assigned to rivaroxaban. The hazard ratio (HR) reflects stratification for endovascular or surgical revascularization. CI, confidence interval.