



Reduction in Acute Limb Ischemia With Rivaroxaban Versus Placebo in Peripheral Artery Disease After Lower Extremity Revascularization: Insights From VOYAGER PAD

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BACKGROUND: Patients with peripheral artery disease (PAD) are at heightened risk of acute limb ischemia (ALI), a thrombotic event associated with amputation, disability, and mortality. Previous lower extremity revascularization (LER) is associated with increased ALI risk in chronic PAD. However, the pattern of risk, clinical correlates, and outcomes after ALI early after LER are not well-studied, and effective therapies to reduce ALI post-LER are lacking.

METHODS: The VOYAGER PAD trial (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD; rNCT02504216) randomized patients with PAD undergoing LER to rivaroxaban 2.5 mg twice daily or placebo on a background of low-dose aspirin. The primary outcome was a composite of ALI, major amputation of vascular cause, myocardial infarction, ischemic stroke, or cardiovascular death. ALI was prospectively ascertained and adjudicated by a blinded committee. The cumulative incidence of ALI was calculated using Kaplan-Meier estimates, and Cox proportional hazards models were used to generate hazard ratios and associated CIs. Analyses were performed as intention-to-treat.

RESULTS: Among 6564 patients followed for a median of 2.3 years, 382 (5.8%) had a total of 508 ALI events. In placebo patients, the 3-year cumulative incidence of ALI was 7.8%. After multivariable modeling, previous LER, baseline ankle-brachial index <0.50, surgical LER, and longer target lesion length were associated with increased risk of ALI. Incident ALI was associated with subsequent all-cause mortality (hazard ratio [HR], 2.59 [95% CI, 1.98–3.39]) and major amputation (HR, 24.87 [95% CI, 18.68–33.12]). Rivaroxaban reduced ALI relative to placebo by 33% (absolute risk reduction, 2.6% at 3 years; HR, 0.67 [95% CI, 0.55–0.82]; $P=0.0001$), with benefit starting early (HR, 0.45 [95% CI, 0.24–0.85]; $P=0.0068$ at 30 days). Benefit was present for severe ALI (associated with death, amputation, or prolonged hospitalization and intensive care unit stay, HR, 0.58 [95% CI, 0.40–0.83]; $P=0.003$) and regardless of LER type (surgical versus endovascular revascularization, P interaction=0.42) or clopidogrel use (P interaction=0.59).

CONCLUSIONS: After LER for symptomatic PAD, ALI is frequent, particularly early after LER, and is associated with poor prognosis. Low-dose rivaroxaban plus aspirin reduces ALI after LER, including ALI events associated with the most severe outcomes. The benefit of rivaroxaban for ALI appears early, continues over time, and is consistent regardless of revascularization approach or clopidogrel use.

Key Words: lower extremity ■ peripheral arterial disease ■ rivaroxaban ■ thrombosis

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Clinical Perspective

What Is New?

- Acute limb ischemia (ALI) after lower extremity revascularization (LER) is common and is associated with poor prognosis.
- Postprocedure risk for ALI manifests early and persists long-term.
- Clinical factors associated with ALI include previous LER, current smoking, lower ankle-brachial index, longer target lesion length, and surgical revascularization.
- Compared with aspirin, low-dose rivaroxaban plus low-dose aspirin reduced the risk of ALI, with benefit apparent early and continued over time and irrespective of LER approach or clopidogrel use.

What Are the Clinical Implications?

- Patients and providers should be made aware of the risk for ALI after LER for symptomatic peripheral artery disease.
- Patient and procedural characteristics may help providers identify patients at high risk for ALI who may benefit from closer monitoring and more intensive medical therapies.
- Early initiation of rivaroxaban plus aspirin after LER and long-term use in patients at low bleeding risk should be considered to prevent ALI.

Nonstandard Abbreviations and Acronyms

ABI	ankle-brachial index
ALI	acute limb ischemia
HR	hazard ratio
ICU	intensive care unit
LER	lower extremity revascularization
PAD	peripheral artery disease
VOYAGER PAD	Vascular Outcomes Study of ASA (Acetylsalicylic Acid) Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD

Patients with peripheral artery disease (PAD) are at risk for cardiovascular and limb ischemic events, including acute limb ischemia (ALI). ALI is characterized by the sudden decrease in limb perfusion that threatens viability of the limb.^{1–3} Analogous to ST-segment–elevation myocardial infarction, ALI is caused by acute thromboembolic occlusion of an artery, and outcomes are determined by anatomic location and extent of thrombosis and time to reperfusion.¹ An initial report of adjudicated ALI in a large randomized trial of medical therapy in PAD came from the TRA2°P-TIMI

50 trial (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50), which examined use of vorapaxar in patients with stable atherosclerotic disease, including PAD, and showed vorapaxar significantly reduced ALI risk.² This definition was adopted and applied in the EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease), which randomized patients with chronic, stable PAD to ticagrelor versus clopidogrel but found no benefit of ticagrelor over clopidogrel.³ These reports were critical in outlining the severity of ALI as an outcome. For example, in patients with PAD in TRA2°P-TIMI 50, ALI was associated with poor outcomes, including prolonged hospitalization in the intensive care unit (ICU) in one-third of patients, major vascular surgery in three-quarters, and death or disability at discharge in 15%.² Observational studies have also reported poor outcomes after ALI.^{4–6}

ALI is a feared complication of lower extremity revascularization (LER) procedures, which are commonly performed to treat symptomatic PAD. Increased risk for ALI has been demonstrated shortly after LER as well as long-term in patients with a remote history of LER.^{2,3,7–11} Despite the morbidity and mortality associated with ALI, the incidence and outcomes of ALI after LER have not been well-studied. As a result, effective therapies to reduce ALI in this setting have been lacking.

In the VOYAGER PAD trial (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD), rivaroxaban 2.5 mg twice daily versus placebo on a background of low-dose aspirin reduced the risk of severe limb and cardiovascular events in 6564 patients with symptomatic PAD undergoing LER.¹² VOYAGER PAD was the first large-scale trial to include ALI in the primary outcome. The effect of rivaroxaban on ALI alone has not been described. Using data from VOYAGER PAD, we therefore sought to understand the risk and factors associated with ALI, understand the prognosis after ALI, and evaluate the effect of rivaroxaban on ALI among patients with PAD undergoing LER.

METHODS

Data Source

Data were from the VOYAGER PAD trial (NCT02504216), the design and results of which have been previously published.^{12,13} VOYAGER PAD was a double-blind trial that randomized 6564 patients with PAD undergoing LER from 542 sites in 34 countries to rivaroxaban 2.5 mg twice daily or placebo on a background of aspirin 100 mg daily. Clopidogrel use 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. All patients provided written, informed consent, and institutional review boards at participating institutions approved the protocols.

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results. VOYAGER PAD enrolled symptomatic patients with PAD ≥ 50 years old and with an abnormal ankle-brachial index (ABI) or toe-brachial index and imaging evidence of PAD distal to the external iliac artery. Eligible patients underwent successful LER for claudication or critical limb ischemia via an endovascular (including hybrid) or surgical approach within the previous 10 days. Key exclusion criteria included a planned course of dual antiplatelet therapy >6 months, clinical indication for systemic anticoagulation, recent ALI or acute coronary syndrome, increased risk of bleeding, significantly impaired baseline renal function, and previous intracranial hemorrhage, stroke, or transient ischemic attack.

Outcomes

The primary efficacy outcome for VOYAGER PAD was a composite of ALI, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death. An independent clinical events committee blinded to treatment assignment adjudicated all deaths and potential ischemic cardiac, cerebrovascular, and vascular limb events, including ALI. ALI was prospectively ascertained and adjudicated using the

following established definition:¹³ sudden worsening of limb perfusion requiring hospitalization and new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis and either of the following: confirmation of arterial obstruction (by imaging, hemodynamics, intraprocedural findings, or pathological evaluation) or treatment with thrombolysis, thrombectomy, or urgent revascularization. For this analysis, severity of ALI was categorized according to subsequent outcomes within 30 days of the ALI event. Severe ALI was defined as any of the following within 30 days of an ALI event: death, major amputation for vascular causes, or peripheral revascularization and hospitalization for ≥ 7 days including at least 1 day in the ICU.

Statistical Analysis

This was a prespecified secondary analysis of VOYAGER PAD. Categorical variables are reported as count (percentage), and continuous variables as median (quartile 1–quartile 3 [Q1–Q3]). Comparisons of baseline characteristics grouped by incident ALI status during follow-up were by Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Given the documented nonlinear relationship between ABI and ischemic events,¹⁴ the relationship between index ABI and incident ALI was characterized using a cubic spline with knots at the 25th, 50th, and 75th percentiles, and the hazard ratio (HR) was set to 1.00 at the median ABI value.

A multivariable proportional hazards model of baseline demographics and clinical characteristics (candidate variables are listed in Table S1) to identify factors associated with ALI was determined by stepwise selection, with P value <0.05 for model entry or exit. Models to estimate the associations between all-cause death and major amputation for vascular causes and incident ALI as a time-varying covariate were determined, with

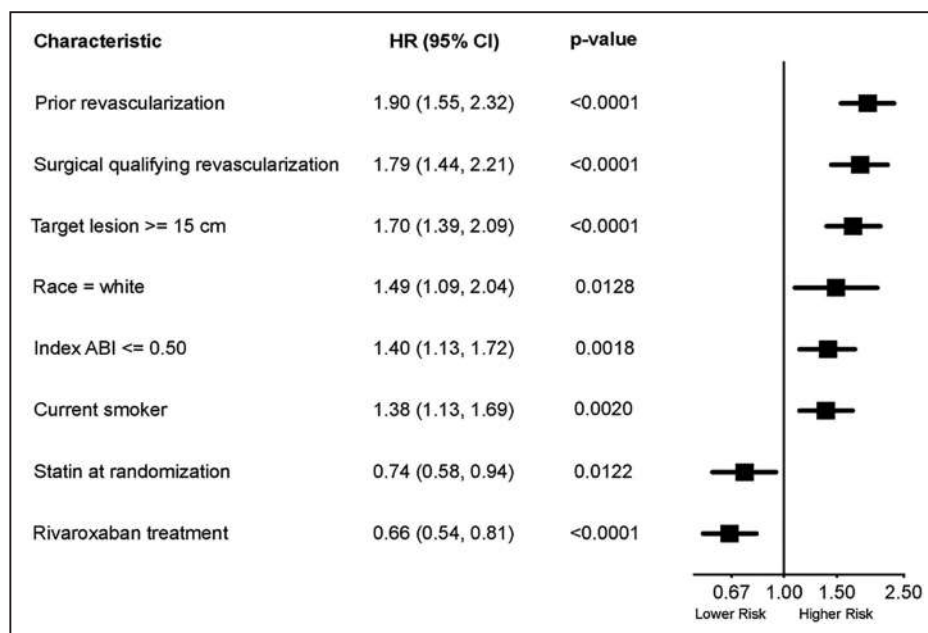


Figure 1. Baseline characteristics associated with acute limb ischemia (ALI).

Baseline patient and procedural characteristics independently associated with ALI after multivariable modeling are shown. Candidate variables included age, sex, White race, current smoker, diabetes, hypertension, hyperlipidemia, heart failure, estimated glomerular filtration rate <60 , coronary artery disease, carotid artery disease, previous revascularization, previous amputation, index ankle-brachial index ≤ 0.50 , systolic blood pressure, statin at randomization, clopidogrel at randomization, endovascular vs, surgical revascularization, indication for revascularization, target lesion ≥ 15 cm, and rivaroxaban treatment. HR indicates hazard ratio.

adjustment for treatment assignment and other baseline factors significantly related to ALI during follow-up (Figure 1) and stratification according to the type of procedure and according to whether clopidogrel was intended to be used. The risk of these events before versus after ALI was also summarized by the number of events per 100 patient-years of follow-up and associated 95% CIs.

On the basis of clinical relevance of the early post-LER time-frame with respect to mechanism of ALI and the observed early separation of treatment curves, a landmark analysis at 30 days was performed. Event probabilities and treatment absolute risk reductions and associated 95% CIs were determined by Kaplan-Meier estimates of cumulative incidence. A sensitivity analysis accounted for death from any cause as a competing terminal event, with incidences estimated by cumulative incidence functions. Possible heterogeneity of the rivaroxaban treatment effect on ALI for subgroups defined by baseline demographic and clinical characteristics was assessed by the significance of interaction terms in proportional hazards models. Analyses of clinical outcomes were performed according to the intention-to-treat principle, including all patients and events from randomization to the study efficacy cut-off date, defined as administrative censoring on September 8, 2019. *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 Characteristics

A total of 6564 patients were randomized and followed for a median of 2.3 (Q1–Q3, 1.8–2.8) years. During the study, a total of 382 (5.8%) patients had a total of 508 ALI events. Baseline characteristics among those who did and did not have an ALI event during follow-up are shown in Tables 1 and 2. Compared with patients without ALI, those with ALI were younger, were more often of White race, and less frequently had diabetes and renal insufficiency. Current smoking, lower baseline ABI, and history of LER before the index revascularization procedure were more common among patients with versus without ALI. As shown in Figure S1, the relationship between index ABI and incident ALI was nonlinear and increased below the median value of 0.56. Patients with ALI more often underwent surgical revascularization, particularly with infrapopliteal bypass targets and prosthetic conduits, were more often treated for CLI, and had longer target lesion length than patients without ALI. Use of statin and clopidogrel at baseline was lower among patients with ALI patients than patients without ALI.

Baseline Characteristics Associated With ALI

After multivariable adjustment (Figure 1), previous LER, surgical LER, longer target lesion length, lower index ABI, and current smoking were all associated with greater ALI risk. In contrast, use of baseline statin and treatment with rivaroxaban versus placebo were independently associated with lower risk of ALI.

Table 1. Baseline Characteristics Stratified by ALI During Study Follow-Up

Characteristic	With ALI	Without ALI	<i>P</i> value
	(N=382)	(N=6182)	
Age, y	65 (59–71)	67 (61–73)	0.0004
Female sex	97 (25.4)	1607 (26.0)	0.86
BMI, kg/m ²	25 (23–28)	26 (23–29)	<0.0001
White race	335 (87.7)	4,968 (80.4)	0.0003
Geographic region			0.0002
North America	39 (10.2)	655 (10.6)	
Western Europe	109 (28.5)	1717 (27.8)	
Eastern Europe	181 (47.4)	2418 (39.1)	
Asia Pacific	27 (7.1)	934 (15.1)	
South America	26 (6.8)	458 (7.4)	
Risk factors and comorbidities			
Current smoker	167 (43.7)	2112 (34.2)	0.0002
Hypertension	303 (79.3)	5039 (81.5)	0.28
Hyperlipidemia	212 (55.5)	3727 (60.3)	0.07
Coronary artery disease	112 (29.3)	1955 (31.6)	0.36
Heart failure	29 (7.6)	510 (8.3)	0.70
Carotid artery disease	28 (7.3)	547 (8.8)	0.35
Atrial fibrillation	13 (3.4)	167 (2.7)	0.42
Diabetes mellitus	122 (31.9)	2507 (40.6)	0.0008
Chronic kidney disease	27 (7.1)	579 (9.4)	0.15
eGFR<60 mL per min per 1.73 m ²	61 (16.0)	1266 (20.5)	0.04
SBP, mm Hg	135 (124–143)	135 (125–145)	0.17
Medications			
Statin	288 (75.4)	4961 (80.3)	0.03
Clopidogrel	164 (42.9)	3149 (50.9)	0.0026
Randomized to rivaroxaban	155 (40.6)	3131 (50.6)	0.0001

Numbers in table are median (quartile 1–quartile 3) or n (%). ALI indicates acute limb ischemia; BMI, body mass index; eGFR, estimated glomerular filtration rate; and SBP, systolic blood pressure.

Outcomes After ALI

Of the 382 patients with at least 1 ALI event, after ALI, 63 (16.5%) died during a median follow-up of 1.8 years (Q1–Q3, 0.9–2.5), and 87 (22.8%) underwent major amputation of vascular etiology during a median follow-up of 1.3 years (Q1–Q3, 0.2–2.2). Across treatment groups, incident ALI was associated with significantly greater risk of subsequent death and major amputation, with marked increases in events per 100 patient-years after versus before an ALI event (all-cause mortality: before ALI, 3.6 [95% CI, 3.3–3.9], after ALI, 9.7 [95% CI, 7.4–12.4]; major amputation: before ALI, 0.9 [95% CI, 0.7–1.0], after ALI, 17.3 [95% CI, 13.8–21.3]; Figure 2). The HR (95% CI) for all-cause death and major amputation after ALI, adjusted for the factors significantly related to ALI during follow-up (Figure 1), was 2.42 (95% CI, 1.85–3.18) and 23.63 (95% CI, 17.59–31.75), respectively. Within

Table 2. Baseline PAD and Procedural Characteristics Stratified by ALI During Study Follow-Up

Characteristic	With ALI	Without ALI	P value
	(N=382)	(N=6182)	
PAD history			
Index ABI \leq 0.50	200 (52.4)	2452 (39.7)	<0.0001
Previous revascularization	185 (48.4)	2151 (34.8)	<0.0001
Previous amputation	21 (5.5)	369 (6.0)	0.82
Qualifying revascularization			
Indication for revascularization			0.02
Claudication	274 (71.7)	4,757 (77.0)	
Critical limb ischemia	108 (28.3)	1,425 (23.1)	
Time from qualifying revascularization to randomization, d	5 (3–7)	5 (2–7)	0.09
Revascularization approach			<0.0001
Endovascular (including hybrid)	189 (49.5)	4190 (67.8)	
Hybrid*	15 (7.9)	273 (6.5)	0.45
Surgical	193 (50.5)	1992 (32.2)	
Location (endovascular)*			0.02
Popliteal or above	166 (87.8)	3665 (87.5)	
Infrapopliteal	16 (8.5)	428 (10.2)	
Other	7 (3.7)	97 (2.3)	
Location (surgical bypass)†			<0.0001
Above-knee popliteal	122 (63.2)	1500 (75.3)	
Below-knee popliteal	53 (27.5)	360 (18.1)	
Tibial/pedal	18 (9.3)	132 (6.6)	
Long (\geq 15 cm) target lesion length	188 (49.2)	2064 (33.4)	<0.0001
Atherectomy*	10 (5.3)	301 (7.2)	0.39
Stent implantation*	99 (52.4)	1172 (42.3)	0.01
Drug-coated device*	69 (36.5)	1289 (30.8)	0.11
Surgery type‡			0.0002
Bypass	120 (62.2)	1004 (50.4)	
Endarterectomy	39 (20.2)	698 (35.0)	
Bypass and endarterectomy	34 (17.6)	290 (14.6)	
Conduit type‡			<0.0001
Vein	38 (25.0)	608 (48.0)	
Prosthetic	114 (75.0)	659 (52.0)	

Numbers in table are median (quartile 1–quartile 3) or n (%). ABI indicates ankle-brachial index; ALI, acute limb ischemia; and PAD, peripheral artery disease.

*Among patients undergoing endovascular revascularization.

†Among patients undergoing surgical revascularization.

‡Among patients undergoing surgical bypass (152 patients with ALI, 1267 patients without ALI).

30 days of an ALI event, 125 of 382 patients with ALI (32.7%) had the most severe subsequent outcomes, including 20 (5.2%) who died, 54 (14.1%) who underwent major amputation, and 51 (13.4%) who underwent revascularization and were hospitalized for \geq 7 days including an ICU stay. The remaining 257 patients with ALI (67.3%)

had the following associated outcomes: 100 (26.2%) requiring revascularization and at least 7 days in the hospital (without ICU stay), 112 (29.3%) patients who underwent revascularization but were hospitalized for $<$ 7 days, and 45 (11.8%) patients who were hospitalized without death, major amputation, or revascularization.

Effect of Rivaroxaban Versus Placebo on ALI

As shown in Figure 3A, at 3 years, the Kaplan-Meier cumulative incidence of ALI was 5.2% and 7.8% for the rivaroxaban and placebo groups, respectively (absolute risk reduction, 2.6% [95% CI, 1.2–3.8]), translating to a number needed to treat of 39 for 3 years. Compared with placebo, treatment with rivaroxaban resulted in a significant reduction in risk for ALI (HR, 0.67 [95% CI, 0.55–0.82]; $P=0.0001$). The relative benefit of rivaroxaban was identical when death from any cause was treated as a competing terminal event (HR, 0.67 [95% CI, 0.55–0.82]; $P=0.0001$), with incidences at 3 years of 5.0% (95% CI, 4.3%–5.8%) and 7.4% (95% CI, 6.5%–8.5%) for rivaroxaban and placebo, respectively. This benefit was apparent within the first month of randomization (HR, 0.45 [95% CI, 0.24–0.85]; $P=0.01$ at 30 days), indicating an early rivaroxaban benefit on ALI (Figure 3B), with continued benefit of rivaroxaban beyond the first 30 days (HR, 0.71 [95% CI, 0.57–0.88]; $P=0.002$). In addition, when ALI events were classified on the basis of severity, rivaroxaban reduced the risk of the most severe ALI events by 42% (HR, 0.58 [95% CI, 0.40–0.83]; $P=0.003$; Figure 4).

Consistency of effect of rivaroxaban was assessed in multiple subgroups (Figure 5). Although all estimated subgroup HRs indicated some degree of benefit by rivaroxaban, there was heterogeneity of effect by age, with potentially greater benefit observed among older patients (P interaction=0.02) and among patients with renal dysfunction (estimated glomerular filtration rate $<$ 60 mL per min per 1.73 m²; P interaction=0.046). The effect of rivaroxaban was consistent irrespective of surgical versus endovascular LER (P interaction=0.71), indication for LER (P interaction=0.78), and baseline clopidogrel use (P interaction=0.59).

DISCUSSION

This analysis of 6564 VOYAGER PAD patients is one of the largest experiences of adjudicated ALI in a randomized trial of patients with PAD undergoing LER to date. The results demonstrate first that ALI is a common complication of LER performed for symptomatic PAD, with risk of ALI manifesting early postprocedure. Second, anatomic, patient, and procedural characteristics, such as lesion length, smoking, and previous LER, are associated with ALI. Third, a large proportion of ALI events is associated with particularly severe outcomes. The prognosis after ALI in general is poor, with increased risk of recurrent ALI, death, and

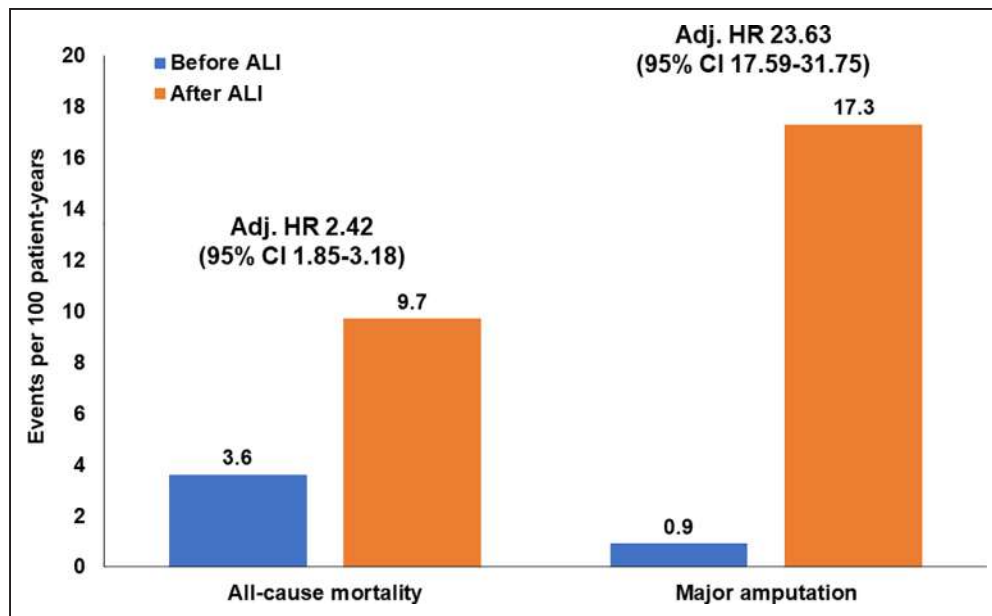


Figure 2. Risk of death and major amputation before versus after incident acute limb ischemia (ALI).

The bar graphs summarize the incidences per 100 patient-years of all-cause death and major amputation for vascular causes before or after incident ALI during the study. HRs and associated CIs summarize the risk of all-cause mortality and major amputation after incident ALI and were estimated from proportional hazards models with incident ALI modeled as a time-varying covariate, with adjustment for treatment assignment, stratification according to the type of procedure and according to whether clopidogrel was intended to be used, and the baseline factors significantly related to ALI during follow-up shown in Figure 1. Adj. indicates adjusted; and HR, hazard ratio.

major amputation after an ALI event, underscoring the importance of prevention. Last, rivaroxaban reduces the risk of ALI, with particularly robust benefit early and for severe ALI events and consistency of effect regardless of revascularization approach or clopidogrel use.

The present study is the first description of ALI as a pre-defined component of a primary efficacy outcome from a large-scale clinical trial of a PAD population undergoing LER. Earlier reports of ALI as a secondary outcome were from cardiovascular outcomes trials studying patients with stable atherosclerotic disease, including PAD,^{2,15,16} as well as studies in chronic, symptomatic PAD.¹⁷ In contrast, VOYAGER PAD enrolled patients undergoing LER for symptomatic PAD, and ALI was a component of the primary outcome, providing a unique opportunity to better understand ALI in this clinical setting.

These data demonstrate that after LER for PAD, there is immediate and early risk for ALI postprocedure. This may be related to endothelial disruption after procedural manipulation and a resultant thrombotic milieu. However, the risk for ALI persists long-term after LER, consistent with the observed \approx 4-fold increased risk of ALI associated with previous LER in stable PAD.²³ History of LER remains an independent predictor of ALI after recent LER, though to a lesser degree (HR, 1.9 [95% CI, 1.55–2.32]), which is likely because of the elevated baseline risk for ALI early postprocedure. Of note, ALI was the most common component of the composite primary outcome in VOYAGER PAD, occurring more frequently than myocardial infarction or ischemic stroke,¹² highlighting

the large burden of limb-specific adverse events, such as ALI, in this patient population. Furthermore, these data demonstrate a high risk of ALI after LER performed for claudication, the most common indication for revascularization in VOYAGER PAD, or critical limb ischemia.

Beyond its high incidence after LER for PAD, ALI is associated with poor prognosis. In the subgroup of patients with chronic, stable PAD enrolled in the Cardiovascular Outcomes for People Using Anticoagulation Strategies trial, the secondary outcome of major adverse limb events was associated with risk of mortality and amputation.¹⁸ In the present study of patients with PAD undergoing LER, mortality after an ALI event was 16.5%. After adjustment for baseline predictors of ALI during follow-up, incident ALI was associated with a 2.4-fold increased risk of death and >20-fold increased risk of major amputation, the latter of which has been associated with significant morbidity, mortality, and cost.^{19,20} In addition, one-third of patients with ALI in the present analysis were classified as having a severe event because of subsequent death, major amputation, or hospitalization for 7 days or more and requiring at least 1 day of ICU care within 30 days after ALI. It is important that more than one-quarter (26.2%) of patients had an ALI event requiring hospitalization at least 7 days without ICU care; these were not classified as severe but still represent a serious event from patient and health care resource perspectives. For comparison, in a recent trial of acute coronary syndromes, over a median of 1.6 years of follow-up, mortality after a type 1 myocardial infarction was

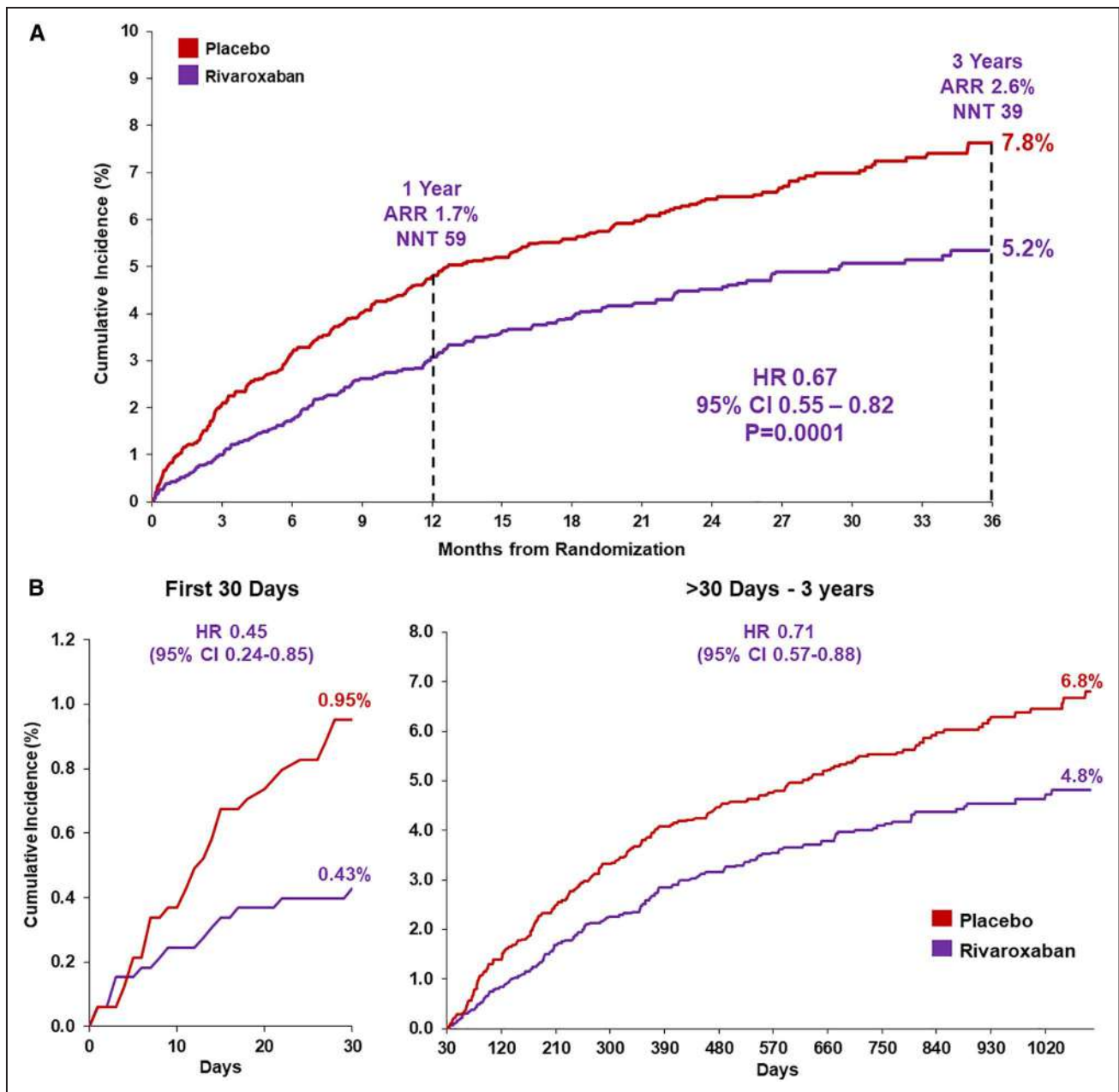


Figure 3. Effect of rivaroxaban on acute limb ischemia (ALI) after lower extremity revascularization.

A, Cumulative incidence curves for ALI in patients assigned to rivaroxaban versus placebo and the hazard ratio (HR) and associated 95% CI. Also shown are the absolute risk reduction (ARR) and number needed to treat (NNT) at 6 months and 3 years. **B**, The curves for rivaroxaban versus placebo during the first 30 days vs >30 days after randomization.

11.9%.²¹ Other analyses have reported that the average hospital lengths of stay after acute myocardial infarction and stroke are 3 and 5 days, respectively,^{22,23} and the median length of stay after coronary artery bypass graft surgery is 5 days.²⁴ Thus, although there is a spectrum of severity of ALI, overall, risks of subsequent mortality and associated health care resource use after ALI appear to be greater than for other cardiovascular conditions.

The high incidence of and poor outcomes after ALI underscore the need for increased awareness of and effective interventions to prevent ALI after LER. Educa-

tion among patients and nonvascular specialty clinicians about ALI symptoms and need for emergent treatment may help reduce late ALI presentations necessitating primary amputation. In addition to history of LER, patient characteristics, such as lower baseline ABI and current smoking, and procedural characteristics, including surgical revascularization and longer target lesion length, may help providers identify patients at greater risk for ALI who may benefit from closer monitoring and more intensive medical therapy. Consistent with previous data in stable PAD,^{2,3,18} current smoking and baseline statin use

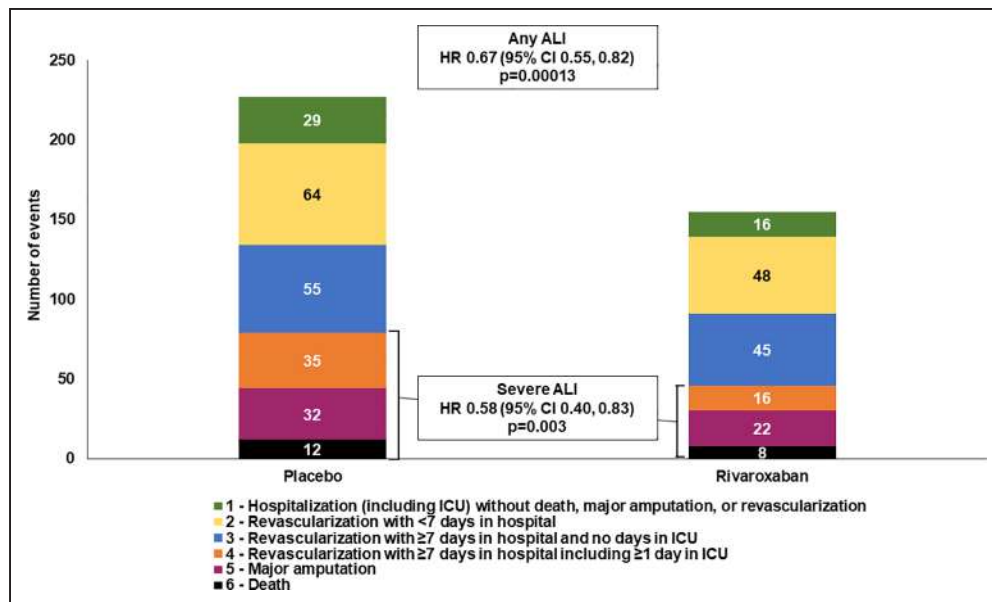


Figure 4. Effect of rivaroxaban on acute limb ischemia (ALI) according to the VOYAGER PAD (Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease) ALI Severity Scale.

Each patient with an ALI event during the study was classified into 1 of 6 categories based on death, major amputation, peripheral revascularization, duration of hospitalization, and need for treatment in the intensive care unit (ICU) occurring within 30 days after the event. HR indicates hazard ratio.

were each associated with increased and decreased risk of ALI after LER, respectively. These findings emphasize the important roles of smoking cessation and medical therapy in optimizing postprocedural limb outcomes. It is important, however, that most patients in VOYAGER PAD were on appropriate background medical therapy, with 80% on baseline statin therapy and all on low-dose aspirin, illustrating the need for additional effective therapies to prevent residual risk of ALI in this setting.

In this analysis, rivaroxaban significantly reduced the risk of ALI overall by 33% when added to aspirin. The benefit of rivaroxaban was consistent across many subgroups, including patients undergoing surgical versus endovascular revascularization and those with versus without baseline clopidogrel use. The efficacy of rivaroxaban was also apparent in each category of ALI severity but was particularly robust for severe events, with a 42% reduction in severe ALI. With respect to timing of benefit, analogous to acute coronary syndromes in which the greatest risk for major adverse cardiovascular events is at the time of presentation, there is significant risk for ALI immediately after LER. This pattern of risk translates into early benefit of rivaroxaban, with a 55% reduction in ALI at 30 days and number needed to treat at 1 year of 59 patients, supporting early initiation of therapy postprocedure. Interestingly, although ALI within 30 days postprocedure is typically considered related to technical errors, our data demonstrate that ALI in this window is modifiable with medical therapies, with particularly robust benefit for ALI reduction with rivaroxaban. Given this early ben-

efit, rivaroxaban plus aspirin could be initiated after LER for PAD before discharge, similar to patients with acute coronary syndromes for whom antithrombotic therapies are started during the hospitalization. It is important that, our data also demonstrate that the benefit of rivaroxaban extends beyond the early period of risk. The persistent risk of ALI and continued benefit of rivaroxaban over time further suggest that not only early initiation but also long-term therapy after LER should be considered.

Although rivaroxaban provides robust reduction in ALI, the risk versus benefit of its use should be considered. In this study, rivaroxaban reduced the absolute risk of ALI by 2.6% at 3 years, for a number needed to treat of 39. In the primary VOYAGER PAD trial, rivaroxaban increased the risk of the primary safety outcome of Thrombolysis in Myocardial Infarction major bleeding (3-year Kaplan-Meier estimate of 2.7% versus 1.9%; HR, 1.43 [95% CI, 0.97–2.10]) with a number needed to harm of 125.¹² Because clinicians using this strategy would do so for prevention of all primary efficacy outcome components, not just ALI, when considering risk-benefit, it is important to note that for 10000 patients treated for 1 year with rivaroxaban, 181 first severe cardiovascular and limb events would be prevented at a cost of 29 Thrombolysis in Myocardial Infarction major bleeding events, translating to a ≈6:1 benefit-risk ratio.¹²

Limitations of this study should be noted. Our analyses identified factors associated with ALI, rather than predictors of ALI.²⁵ Although adjusted models accounted for known baseline characteristics, postrandomization variables were not included, and residual confounding

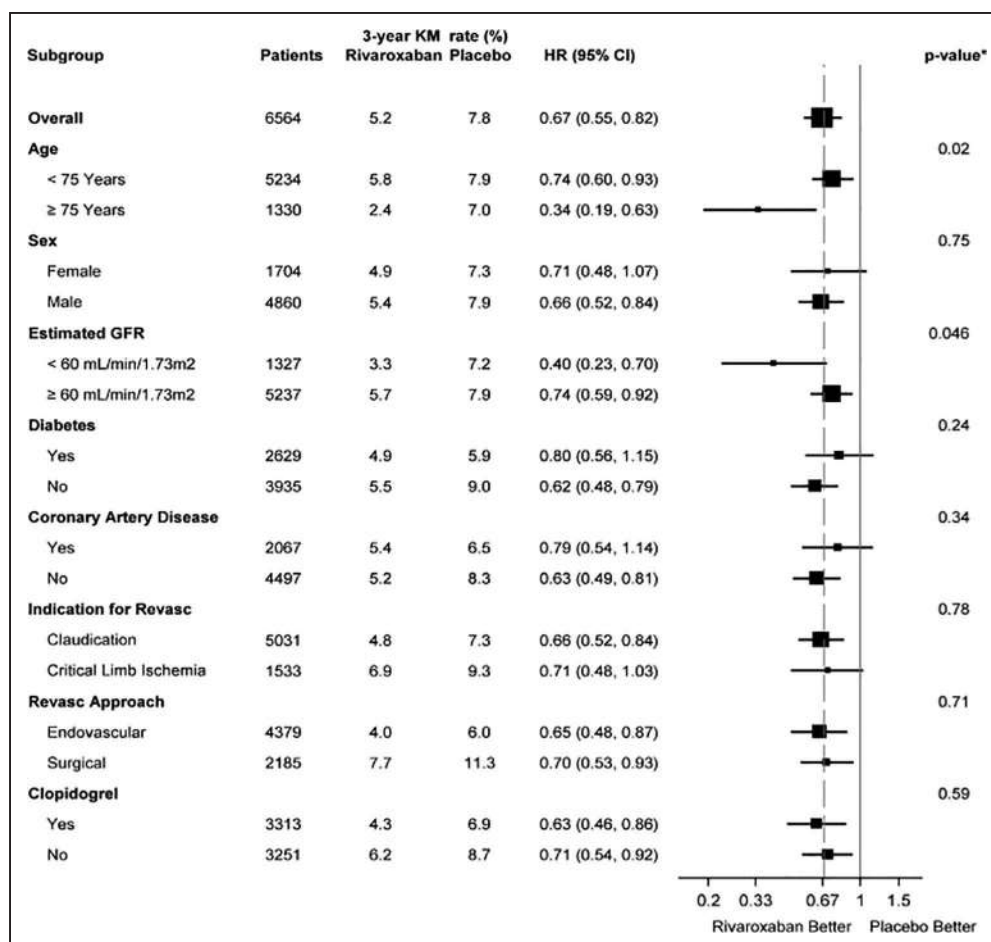


Figure 5. Effect of rivaroxaban on acute limb ischemia in selected subgroups.

GFR indicates glomerular filtration rate; HR, hazard ratio; KM, Kaplan-Meier; and Revasc, revascularization. **P* values from tests of interactions between treatment and subgroups.

may exist. Outcomes after events (eg, death after ALI) are not necessarily caused by the proximate events, and observations should be treated as associations. Finally, ICU care and hospital length of stay were used to identify severe ALI events, and these metrics may be influenced not only by severity of illness but also by local practice patterns and resource availability.

Conclusions

Patients undergoing LER for symptomatic PAD are at heightened risk for ALI, both early and long-term after the procedure, and prognosis after ALI is poor, with increased risk of subsequent death and major amputation. Patient and procedural characteristics may help providers identify high-risk patients who may benefit from more intensive monitoring and therapy. Rivaroxaban significantly reduced risk of ALI overall, with robust benefit observed early after LER and for severe ALI events and with consistent effect irrespective of revascularization approach and baseline clopidogrel use.

ARTICLE INFORMATION

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Supplemental Material

Table S1

Figure S1

REFERENCES

- Creager MA, Kaufman JA, Conte MS. Clinical practice: acute limb ischemia. *N Engl J Med*. 2012;366:2198–2206. doi: 10.1056/NEJMc1006054
- Bonaca MP, Gutierrez JA, Creager MA, Scirica BM, Olin J, Murphy SA, Braunwald E, Morrow DA. 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. doi: 10.1161/CIRCULATIONAHA.115.019355
- Hess CN, Huang Z, Patel MR, Baumgartner I, Berger JS, Blomster JI, Fowkes FGR, Held P, Jones WS, Katona B, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140:556–565. doi: 10.1161/CIRCULATIONAHA.119.039773
- Davis FM, Albright J, Gallagher KA, Gurm HS, Koenig GC, Schreiber T, Grossman PM, Henke PK. Early outcomes following endovascular, open surgical, and hybrid revascularization for lower extremity acute limb ischemia. *Ann Vasc Surg*. 2018;51:106–112. doi: 10.1016/j.avsg.2017.12.025
- Kolte D, Kennedy KF, Shishehbor MH, Mamdani ST, Stangenberg L, Hyder ON, Soukas P, Aronow HD. Endovascular versus surgical revascularization for acute limb ischemia: a propensity-score matched analysis. *Circ Cardiovasc Interv*. 2020;13:e008150. doi: 10.1161/CIRCINTERVENTIONS.119.008150
- Baril DT, Ghosh K, Rosen AB. Trends in the incidence, treatment, and outcomes of acute lower extremity ischemia in the United States Medicare population. *J Vasc Surg*. 2014;60:669–677.e2. doi: 10.1016/j.jvs.2014.03.244
- Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol*. 2016;67:2719–2728. doi: 10.1016/j.jacc.2016.03.524
- Hess CN, Wang TY, Weleski Fu J, Gundrum J, Allen LaPointe NM, Rogers RK, Hiatt WR. Long-term outcomes and associations with major adverse limb events after peripheral artery revascularization. *J Am Coll Cardiol*. 2020;75:498–508. doi: 10.1016/j.jacc.2019.11.050
- Hess CN, Rogers RK, Wang TY, Fu R, Gundrum J, Allen LaPointe NM, Hiatt WR. Major adverse limb events and 1-year outcomes after peripheral artery revascularization. *J Am Coll Cardiol*. 2018;72:999–1011. doi: 10.1016/j.jacc.2018.06.041
- Jones WS, Baumgartner I, Hiatt WR, Heizer G, Conte MS, White CJ, Berger JS, Held P, Katona BG, Mahaffey KW, et al; International Steering Committee and Investigators of the EUCLID Trial. Ticagrelor compared with clopidogrel in patients with prior lower extremity revascularization for peripheral artery disease. *Circulation*. 2017;135:241–250. doi: 10.1161/CIRCULATIONAHA.116.025880
- Moussa Pacha H, Mir T, Al-Khadra Y, Sattar Y, Ullah W, Zaher N, Ahmad B, M Suleiman AR, Darmoch F, Soud M, et al. Trends and causes of readmission following peripheral vascular intervention in patients with peripheral vascular disease. *Catheter Cardiovasc Interv*. 2021;98:540–548. doi: 10.1002/ccd.29698
- 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
- Capell WH, Bonaca MP, Nehler MR, Chen E, Kittelson JM, Anand SS, Berkowitz SD, Debus ES, Fanelli F, Haskell L, 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. doi: 10.1016/j.ahj.2018.01.011
- Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al; Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208. doi: 10.1001/jama.300.2.197
- 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 (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235
- Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol*. 2016;67:2719–2728. doi: 10.1016/j.jacc.2016.03.524
- Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, et al; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40. doi: 10.1056/NEJMoa1611688
- Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315. doi: 10.1016/j.jacc.2018.03.008
- Whittaker JD, Tullett R, Patel N, Newman J, Garnham A, Wall M. Short-term mortality, morbidity and recovery milestones after major lower limb amputation: a prospective evaluation of outcomes in a tertiary center. *Ann Vasc Surg*. 2019;56:261–273. doi: 10.1016/j.avsg.2018.07.070
- Tang L, Paravastu SCV, Thomas SD, Tan E, Farmer E, Varcoe RL. Cost analysis of initial treatment with endovascular revascularization, open surgery, or

primary major amputation in patients with peripheral artery disease. *J Endovasc Ther.* 2018;25:504–511. doi: 10.1177/1526602818774786

21. White HD, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Erglis A, Goodman SG, Hanotin C, et al; ODYSSEY OUTCOMES Investigators. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. *Eur Heart J.* 2019;40:2801–2809. doi: 10.1093/eurheartj/ehz299
22. Cowper PA, Knight JD, Davidson-Ray L, Peterson ED, Wang TY, Mark DB; TRANSLATE-ACS Investigators. Acute and 1-year hospitalization costs for acute myocardial infarction treated with percutaneous coronary intervention: results from the TRANSLATE-ACS Registry. *J Am Heart Assoc.* 2019;8:e011322. doi: 10.1161/JAHA.118.011322
23. Hall MJ, Levant S, DeFrances CJ. Hospitalization for stroke in U.S. hospitals, 1989–2009. *NCHS Data Brief.* 2012;95:1–8.
24. Haddad DN, Shipe ME, Absi TS, Danter MR, Vyas R, Levack M, Shah AS, Grogan EL, Balsara KR. Preparing for bundled payments: impact of complications post-coronary artery bypass grafting on costs. *Ann Thorac Surg.* 2021;111:1258–1263. doi: 10.1016/j.athoracsur.2020.06.105
25. Shmueli G. To explain or to predict? *Statist Sci* 2010;25:289–310. doi: 10.1214/10-STS330



The University of Tokyo Hospital, Tokyo, Japan

The origin of the University of Tokyo Hospital and Faculty of Medicine dates back to the year 1858 when the Otamagaike smallpox vaccination center was founded. After a series of changes in name and location, and a merger with Tokyo Kaisei School, the University of Tokyo was born in 1877 as the first national university in Japan. The picture on the **top left** depicts the Main Building of the Medical School in 1879. From the earliest days of modern medicine in Japan, the University of Tokyo Hospital has contributed to the development of medical practice and research and produced outstanding medical professionals and researchers. Sunao Tawara (1873–1952) (**top middle**) discovered atrioventricular conduction of excitation in the heart at Ludwig Ashoff's laboratory in Marburg. Setsuro Ebashi (1922–2006) (**top right**) discovered troponin and uncovered the regulatory role of calcium ions in muscle contraction and relaxation. The **bottom** image is a current panoramic view of the University of Tokyo Hospital. The hospital houses 1226 beds with a total of approximately 4300 staff members. It continues to provide advanced and specialized medical care, including heart transplantation, develop advanced medical technology, and cultivate excellent health care professionals.

Images courtesy of the Medical Library, Graduate School of Medicine and Faculty of Medicine, the University of Tokyo.

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