Circulation

ORIGINAL RESEARCH ARTICLE

Acute Limb Ischemia in Peripheral Artery Disease

Insights From EUCLID

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BACKGROUND: Acute limb ischemia (ALI) is an important clinical event and an emerging cardiovascular clinical trial outcome. Risk factors for and outcomes after ALI have not been fully evaluated.

METHODS: EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) randomized patients with peripheral artery disease to ticagrelor versus clopidogrel. Enrollment criteria included an ankle-brachial index ≤0.80 or previous lower extremity revascularization. Patients were grouped according to the primary outcome, postrandomization ALI hospitalization. Baseline factors associated with ALI were identified using Cox proportional hazards modeling. Models with ALI hospitalization as a time-dependent covariate were developed for secondary outcomes of major adverse cardiovascular events (myocardial infarction, cardiovascular death, ischemic stroke), all-cause mortality, and major amputation.

RESULTS: Among 13 885 patients, 1.7% (n=232) had 293 ALI hospitalizations (0.8 per 100 patient-years). Patients with versus without ALI were younger and more often had previous peripheral revascularization and lower baseline ankle-brachial index. Treatment during ALI hospitalization included endovascular revascularization (39.2%, n=115), surgical bypass (24.6%, n=72), and major amputation (13.0%, n=38). After multivariable adjustment, any previous peripheral revascularization (Hazard Ratio [HR] 4.7, 95% CI 3.3–6.8, *P*<0.01), baseline atrial fibrillation (HR 1.8, 95% CI 1.1–3.2, *P*=0.03), and baseline ankle-brachial index ≤0.60 (HR 1.3 per 0.10 decrease, 95% CI 1.1–1.5, *P*<0.01) were associated with higher ALI risk. Older age (HR 0.8 per 10-year increase, 95% CI 0.7–1.0, *P*=0.02) and baseline statin use (HR 0.7, 95% CI 0.5–0.9, *P*<0.01) were associated with lower risk for ALI. There was no relationship between randomized treatment to ticagrelor or clopidogrel and ALI. Among patients with previous revascularization, surgical versus endovascular procedures performed more than 6 months prior were associated with ALI (adjusted HR 2.63, 95% CI 1.75–3.96). In the overall population, ALI hospitalization was associated with subsequent MACE (adjusted HR 1.4, 95% CI 1.0–2.1, *P*=0.04), all-cause mortality (adjusted HR 3.3, 95% CI 2.4–4.6, *P*<0.01), and major amputation (adjusted HR 34.2, 95% CI 9.7–20.8, *P*<0.01).

CONCLUSIONS: Previous peripheral revascularization, baseline atrial fibrillation, and lower ankle-brachial index identify peripheral artery disease patients at heightened risk for ALI, an event associated with subsequent cardiovascular and limb-related morbidity and mortality.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01732822.

Key Words: peripheral arterial disease ■ treatment outcome

Sources of Funding, see page 563

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- This subgroup analysis of EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) is the first to assess acute limb ischemia (ALI) in the context of a large-scale clinical trial studying a primary peripheral artery disease (PAD) population.
- ALI occurred in 1.7% of 13 885 randomized patients, with a median time to hospitalization for ALI of 320 days after randomization.
- In this population, previous lower extremity revascularization, atrial fibrillation, and lower ankle-brachial index identified patients at higher risk for ALI.
- Hospitalization for ALI was associated with subsequent cardiovascular and limb ischemic events.

What Are the Clinical Implications?

- Providers should monitor for signs and symptoms of ALI in patients with stable, symptomatic PAD, particularly those with previous lower extremity revascularization, atrial fibrillation, and lower ankle-brachial index.
- Efforts to mitigate the onset of ALI and associated risk of cardiovascular and limb events are needed.

Peripheral artery disease (PAD), which typically refers to atherosclerotic arterial disease of the lower extremities, affects more than 200 million people worldwide.[1] PAD is considered a clinical manifestation of systemic atherosclerosis and is often present with concomitant coronary artery disease and cerebrovascular disease.[2–4] Multiple studies have demonstrated a high risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular death, among patients with PAD.[5–7] Beyond cardiovascular outcomes, patients with PAD are also at risk for ischemic limb events which can cause significant morbidity and reduce functional status and quality of life.[8–10] In particular, acute limb ischemia (ALI) resulting from a sudden decrease in limb perfusion can lead to tissue loss and threaten limb viability.

Given the significant morbidity associated with this vascular emergency, ALI is also an emerging outcome in cardiovascular clinical trials, but it has not yet been fully evaluated. Clinical trials examining antithrombotic therapies to reduce MACE have included patients with PAD,[3,11–15] and some trials have been conducted in primary PAD populations.[16–18] However, many of these studies did not report limb outcomes and did not adjudicate these outcomes. EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) was a randomized cardiovascular clinical trial that included ALI as an adjudicated outcome in a primary PAD population.[4] In EUCLID, ticagrelor was not superior to clopidogrel for the prevention of cardiovascular events in patients with stable PAD. However, a EUCLID subgroup analysis of patients with and without previous limb revascularization demonstrated significantly higher risk for ALI hospitalization in patients with previous lower extremity revascularization.[19] Data from EUCLID therefore provide a unique opportunity to 1) compare patients with and without hospitalization for ALI, 2) characterize ALI events, 3) identify factors associated with ALI hospitalization, and 4) examine subsequent cardiovascular and limb outcomes occurring after hospitalization for ALI.

METHODS

Data Source

Data for this analysis were from the EUCLID trial (NCT01732822), the design and results of which has been previously published.[4,20] In brief, EUCLID was a double-blind, event-driven trial that randomized 13 885 patients with stable PAD from 811 study sites in 28 countries to ticagrelor 90 mg twice daily or clopidogrel 75 mg daily as antiplatelet monotherapy to assess the effect of these regimens on cardiovascular and limb events. The clinical database was managed by the Duke Clinical Research Institute (Durham, NC), which also conducted all analyses for publication. An independent clinical events classification committee whose members were unaware of treatment assignment adjudicated all primary efficacy and safety outcomes, and safety oversight was provided by an independent data monitoring committee. Written, informed consent was obtained from all patients, and institutional review boards for participating institutions approved protocols.

As EUCLID was designed and completed before the requirement to make all source data publicly available, the authors declare that all supporting data were available to the authors but will not be made available to other researchers. Dr Hess had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Study Population

Patients ≥50 years of age with lower extremity PAD were enrolled in EUCLID based on either an abnormal ankle-brachial index (ABI) ≤0.80 at screening or a previous revascularization of the lower extremity more than 30 days before randomization. Patients with current or planned use of dual antiplatelet therapy or aspirin, those at high risk for bleeding, and those receiving anticoagulant treatment were excluded, as were patients with a planned revascularization or major amputation within 3 months.

Outcomes

The primary outcome for this analysis was time to hospitalization for ALI. Secondary outcomes included time to MACE and its individual components, all-cause mortality, and major lower extremity amputation. Hospitalization for ALI was defined as a hospitalization with a rapid or sudden decrease in limb perfusion plus either 1) a new pulse deficit, rest pain, pallor, paresthesia, or paralysis; or 2) confirmation of arterial

obstruction by limb hemodynamics (ankle or toe pressure), imaging, intraoperative findings, or pathological evaluation.

Statistical Analysis

Patients were pooled across ticagrelor and clopidogrel treatment arms and grouped according to whether a hospitalization for ALI occurred. Potential baseline risk factors for ALI were first identified a priori by the authors based on clinical judgment and published literature (Table 1).[21] Baseline characteristics were presented for subjects with and without an ALI hospitalization. Univariable Cox regression models were used to assess the relationship between each baseline characteristic and ALI, and *P*-values were presented. Among patients with an ALI hospitalization, presenting characteristics of the ALI event were described. Baseline factors with a *P*-value ≤0.25 in the univariable Cox regression models were considered for inclusion in multivariable models. Functional forms of continuous factors were examined, and linear splines were created when appropriate. To build a parsimonious model, correlation among risk factors was assessed using Pearson's and polychoric/tetrachoric correlation tests for continuous and categorical variables, respectively. If two risk factors were strongly correlated (correlation coefficient ≥0.70), one was selected based on clinical judgment for inclusion in the model. Stepwise selection was carried out, and variables with *P*-values ≤0.05 were kept in the model. Interactions between risk factors were evaluated and included according to clinical relevance. Study treatment was added into the final model.

Postrandomization cardiovascular and limb outcomes among patients with and without ALI hospitalization were described. The relationship between MACE and ALI was explored using a Cox proportional hazards model with MACE as the outcome and ALI treated as a time-dependent covariate. For patients with MACE before an ALI event, they were considered as having reached the outcome without ALI. In this framework, hazard ratios (HR) for ALI hospitalization for MACE, its individual components, all-cause mortality, and major amputation were estimated with adjustment for baseline covariates.

In models the potential impact of competing risk of death to non-fatal events was adjusted by the Fine and Gray method. *P*-values were not adjusted for multiple testing, and all analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 13 885 patients with PAD randomized in EUCLID, 1.7% (n=232) had a total of 293 ALI hospitalizations, with a median time to hospitalization of 320 days (25th, 75th percentiles: 122, 610) after randomization (Figure 1). The overall exposure-adjusted event rate for ALI hospitalization was 0.8 per 100 patient-years.

Baseline Characteristics

Table 1 shows baseline patient characteristics according to ALI hospitalization. Compared with patients without ALI, those with ALI were younger, had lower body mass index, more frequently had a previous lower extremity revascularization (84.5% vs. 56.2%; *P*<0.001) or amputation (11.6% vs. 6.5%; *P*<0.01) before randomization, and had lower baseline ABI values (mean 0.71±0.25 vs. 0.78±0.23). Patients with and without ALI after randomization had similar prevalence of medical comorbidities, with the exception of hyperlipidemia, which was less prevalent among patients with ALI. Patients with ALI were less frequently taking baseline statins than patients without ALI.

Procedure characteristics for patients enrolled based on previous revascularization inclusion criteria (n=7875) were described according to hospitalization for ALI (Table 2). Within this subgroup, compared with patients without ALI, patients with ALI more often had a history of recent revascularization within 30 days to 6 months before randomization and more often underwent surgical versus endovascular peripheral revascularization, with 25.5% undergoing previous above-knee femoral popliteal bypass surgery, and 16.3% undergoing previous below-knee femoral popliteal bypass surgery.

Presentation Characteristics of ALI Hospitalizations

During 293 hospitalizations for ALI, patients presented with a variety of symptoms, including rest pain (71.3%, n=271), pallor (10.2%, n=30), parasthesias (7.5%, n=22), and paralysis (2.4%, n=10). Acute arterial obstruction was confirmed by catheter-based angiography (55.6%, n=163), ultrasonography (46.1%, n=135), computed tomographic angiography (22.5%, n=66), limb hemodynamic testing (8.2%, n=24), and magnetic resonance angiography (3.1%, n=9). Common treatment strategies for ALI included endovascular revascularization (39.2%, n=115), surgical bypass (24.6%, n=26), and embolectomy (31.0%, n=91). Major amputation was performed in 13% (n=38) of hospitalizations and consisted of above-knee amputation (10.9%, n=32) and below-knee amputation (2.0%, n=6); foot or ray amputations occurred in 2.4% (n=7) of hospitalizations.

Factors Associated With Hospitalization for ALI

After multivariable modeling, we identified baseline factors associated with hospitalization for ALI in the overall study population (Table 3; c-index 0.72). Previous lower extremity revascularization (adjusted HR 4.7, 95% CI 3.3–6.8, *P*<0.01), previous atrial fibrillation (adjusted HR 1.8, 95% CI 1.1–3.2, *P*=0.03), and baseline ABI value ≤0.60 (adjusted HR 1.3 for every 0.1 decrease in ABI, 95% CI 1.1–1.5, *P*<0.01) were significantly associated with higher ALI risk. Lower risk of ALI

Table 1. Baseline Characteristics According to Hospitalization for ALI

	ALI (n=232)	No ALI (n=13653)	*P* Value
Age, median (25th, 75th), y	64.0 (59.0, 70.5)	66.0 (60.0, 73.0)	0.02
Female sex, n (%)	62 (26.7)	3826 (28.0)	0.65
BMI, median (25th, 75th), kg/m^2	25.6 (22.7, 29.8)	26.8 (23.9, 30.1)	<.01
Region, n (%)			0.02
North America	56 (24.1)	2989 (21.9)	
Europe	140 (60.3)	7358 (53.9)	
Asia	23 (9.9)	1579 (11.6)	
Central/South America	13 (5.6)	1727 (12.6)	
Inclusion criterion			
Previous lower extremity revascularization, n (%)	196 (84.5)	7679 (56.2)	<.001
ABI value, mean (±SD)	0.71 (± 0.25)	0.78 (± 0.23)	<.01
ABI/TBI criteria, n (%)	36 (15.5)	5974 (43.8)	<.001
ABI value, mean (±SD)	0.57 (± 0.15)	0.63 (± 0.15)	0.02
TBI value, mean (±SD)	0.48 (± 0.17)	0.52 (± 0.22)	
Limb symptoms at study entry			0.07
Asymptomatic	52 (22.4)	2549 (18.7)	
Mild/moderate claudication	110 (47.4)	7300 (53.5)	
Severe claudication	53 (22.8)	3175 (23.3)	
Critical limb ischemia			0.13
Rest pain	9 (3.9)	369 (2.7)	
Minor tissue loss (ischemic ulceration not exceeding ulcer of the digits of the foot)	6 (2.6)	201 (1.5)	
Major tissue loss (severe ischemic ulcers or frank gangrene)	2 (0.9)	56 (0.4)	
Previous amputation*	27 (11.6)	894 (6.5)	0.004
Major amputation above the ankle	8 (3.4)	331 (2.4)	
Above knee amputation	4 (1.7)	198 (1.5)	
Below knee amputation	23 (9.9)	696 (5.1)	
Transtibial amputation	4 (1.7)	133 (1.0)	
Ankle disarticulation	1 (0.4)	9 (0.1)	
Partial foot amputation	3 (1.3)	86 (0.6)	
Toe amputation	15 (6.5)	468 (3.4)	
Medical history, n (%)			
History of stroke	24 (10.3)	1119 (8.2)	0.20
History of TIA	9 (3.9)	498 (3.6)	0.86
Previous MI	42 (18.1)	2480 (18.2)	0.94
Previous PCI or CABG	53 (22.8)	3166 (23.2)	0.90
Number of diseased vascular beds			0.75
1	136 (58.6)	7668 (56.2)	
2	73 (31.5)	4615 (33.8)	
3	23 (9.9)	1370 (10.0)	
Diabetes mellitus	82 (35.3)	5263 (38.5)	0.32
Hypertension	172 (74.1)	10685 (78.3)	0.13
Hyperlipidemia	155 (66.8)	10325 (75.6)	<.01
Congestive heart failure	25 (10.8%)	1903 (13.9%)	0.21
Atrial fibrillation	15 (6.5%)	481 (3.5%)	0.01
Tobacco use			0.12

(*Continued*)

Table 1. Continued

	ALI (n=232)	No ALI (n=13653)	*P* Value
Never smoked	41 (17.7)	2943 (21.6)	
Current smoker	85 (36.6)	4204 (30.8)	
Former smoker	105 (45.3)	6425 (47.1)	
Medications at baseline, n (%)			
Aspirin	161 (69.4)	9110 (66.7)	0.39
Clopidogrel	100 (43.1)	4373 (32.0)	<.001
Statin	154 (66.4)	10027 (73.4)	0.02
ACE inhibitor	101 (43.5)	5534 (40.5)	0.36
ARB	39 (16.8)	3449 (25.3)	<.01
β-blocker	83 (35.8)	5557 (40.7)	0.13

ABI indicates ankle-brachial index; ACE, angiotensin converting enzyme; ALI, acute limb ischemia; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; TBI, toe-brachial index; and TIA, transient ischemic attack.

*Patients may have had ≥1 type of amputation.

was associated with older age (adjusted HR 0.8, 95% CI 0.7–1.0, *P*=0.02) and baseline statin use (adjusted HR 0.7, 95% CI 0.5–0.9, *P*<0.01). There was no relationship between randomized treatment to ticagrelor or clopidogrel and postrandomization ALI.

Baseline factors associated with ALI hospitalization were also examined among the 7875 patients enrolled based on previous limb revascularization (Table in the Online-only Data Supplement; c-index 0.70). There was a significant interaction between type and timing of previous revascularization ($P_{interaction}$=0.01), whereby surgical versus endovascular revascularization more than 6 months before randomization was significantly associated with ALI (adjusted HR 2.7, 95% CI 1.8–4.0). Among patients with baseline ABI ≤0.60, every 0.1 decrease in ABI was associated with higher risk of ALI (adjusted HR 1.3, 95% CI 1.1–1.5, *P*<0.01), whereas baseline statin use was associated with lower ALI risk (adjusted HR 0.7, 95% CI 0.5–1.0, *P*=0.02).

Subsequent Events After Hospitalization for ALI

The frequency and timing of postrandomization cardiovascular and limb events were examined among patients with and without ALI. As shown in Table 4, the rate of postrandomization MACE was higher for patients with versus without ALI, with the majority of MACE occurring after an ALI event. Higher event rates for patients with ALI, with most events occurring post-ALI, were also seen for myocardial infarction, ischemic stroke, and major amputation. All-cause mortality and cardiovascular mortality were more common among patients with ALI than those without (18.5% vs. 8.9% and 11.2% vs. 5.0%, respectively). Among the 232 patients with ALI, 7.3% (n=17) had a total of 52 repeat hospitalizations for ALI, 41.3% (n=96) underwent a subsequent peripheral revascularization, and 19.4% (n=45) had a subsequent amputation.

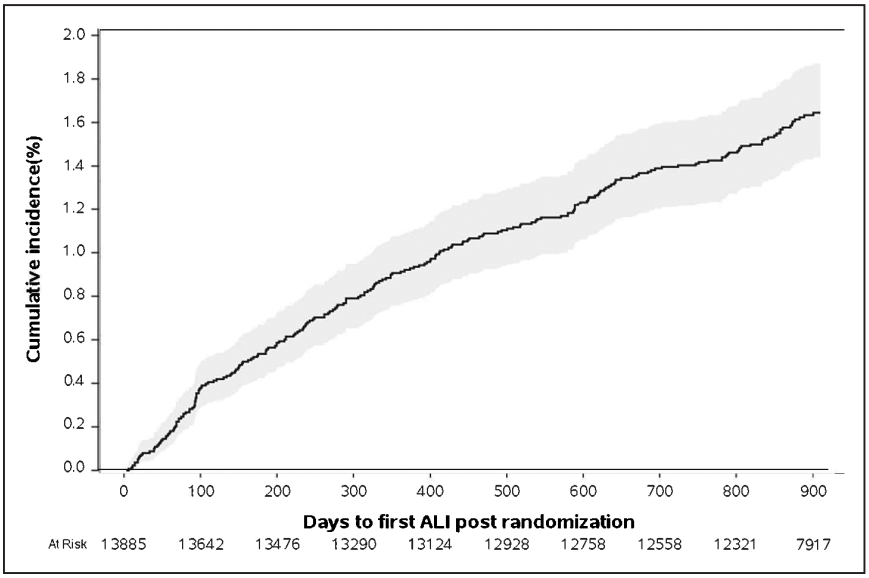

Figure 1. Postrandomization hospitalization for ALI.
Shown is the cumulative incidence of hospitalization for acute limb ischemia (ALI) after randomization. The associated 95% confidence interval is shaded.

Table 2. Procedure Characteristics Among Patients With Previous Lower Limb Revascularization According to Hospitalization for ALI

	ALI (n=196)	No ALI (n=7679)	*P* Value
Type of previous revascularization			<.01
Surgical	105 (53.6)	2757 (35.9)	
Endovascular	91 (46.4)	4912 (64.0)	
Anatomic location of prior endovascular revascularization			
Iliac	51 (26.0)	2623 (34.2)	
CFA	20 (10.2)	609 (7.9)	
SFA	70 (35.7)	2609 (34.0)	
Popliteal	41 (20.9)	899 (11.7)	
Tibial	10 (5.1)	529 (6.9)	
Type of previous surgical revascularization			
Endarterectomy (CFA/SFA)	33 (16.8)	761 (9.9)	
Aorto-bifemoral bypass	26 (13.3)	754 (9.8)	
Axillary bifemoral bypass	5 (2.6)	80 (1.0)	
Femoral popliteal bypass (above knee)	50 (25.5)	964 (12.6)	
Femoral popliteal bypass (below knee)	32 (16.3)	637 (8.3)	
Other	25 (12.8)	684 (8.9)	
Time since most recent lower extremity revascularization			<.01
>30 days to ≤6 months	84 (42.9)	2369 (30.9)	
>6 months to ≤2 years	57 (29.1)	2412 (31.4)	
>2 years	54 (27.6)	2838 (37.0)	

ALI indicates acute limb ischemia; CFA, common femoral artery; and SFA, superficial femoral artery.

After multivariable modeling (Figure 2), ALI hospitalization was associated with subsequent higher risk of MACE (adjusted HR 1.4, 95% CI 1.0–2.1, *P*=0.04) and its individual components, as well as all-cause mortality (adjusted HR 3.3, 95% CI 2.4–4.6, *P*<0.01) and major amputation (adjusted HR 14.2, 95% CI 9.7–20.8, *P*<0.01). There was no relationship between ALI and randomized treatment to ticagrelor versus clopidogrel for each outcome ($P_{interaction}$ >0.15 for all).

DISCUSSION

In this study of 13 885 patients with symptomatic PAD enrolled in EUCLID, the prognosis after ALI was extremely poor, with a 1.4-fold greater risk of MACE, 3.3-fold greater risk of all-cause mortality, and 14.2-fold greater risk of major amputation. Factors associated with higher ALI risk included any previous lower extremity revascularization, previous atrial fibrillation, and lower baseline ABI values, whereas older age and baseline statin use were associated with lower risk for ALI. Among patients with a history of peripheral revascularization, ALI risk was greatest for those who underwent surgical revascularization performed more than 6 months before randomization. These findings build on previous observations that a lower extremity revascularization is a major risk factor for ALI.[21] Whether the revascularization procedure per se is causal for this increased risk or whether a previous revascularization simply reflects a high risk patient is not known. However, new medical treatments to reduce the risk of ALI, including in the immediate postrevascularization setting, are under study.[22–24]

Before EUCLID, large clinical cardiovascular trials of antithrombotic therapies had not examined ALI as an outcome in a primary PAD population. An older trial studying the use of oral anticoagulation was conducted in patients with PAD and reported adjudicated limb outcomes but did not include ALI as an outcome.[15] Although ALI was reported and adjudicated in the TRA2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events - Thrombolysis in Myocardial Infarction 50) and COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trials, patients with PAD in these studies were subgroups of primarily coronary artery disease patient populations.[13,14] In TRA2°P-TIMI 50, 26 449 patients with stable atherosclerotic vascular disease (history of myocardial infarction or ischemic stroke within the previous 2 weeks to 12 months or symptomatic PAD) were randomized to vorapaxar versus placebo. In the subgroup of patients enrolled based on symptomatic PAD (n=3787) and randomized to placebo, the rate of first ALI was 1.3% per year.[21] Compared with placebo and mainly on a background of antiplatelet therapy (96% to 97%), vorapaxar reduced first ALI events by 41% (HR 0.58, 95% CI 0.39–0.86; *P*=0.006). The COMPASS trial randomized 27 395 patients with stable atherosclerosis (coronary artery disease or PAD, including carotid artery disease) to rivaroxaban alone, low-dose rivaroxaban plus aspirin, or aspirin alone.[14] In a subgroup analysis of 7470 patients with PAD with a median follow-up of 21 months, the rate of ALI among patients randomized to aspirin alone was 0.8% per year.[22] Low-dose rivaroxaban plus aspirin (HR 0.56, 95% CI 0.32–0.99; *P*=0.042) and rivaroxaban alone (HR 0.57, 95% 0.32–1.00; *P*=0.046) significantly reduced rates of ALI compared with aspirin alone.

In our study, the rate of ALI in the overall EUCLID population of chronic, symptomatic PAD was comparable to rates observed in the PAD subgroups in TRA2°P-TIMI 50 and COMPASS. However, unlike the reductions in ALI associated with vorapaxar versus placebo and rivaroxaban versus aspirin, in EUCLID, which was an overall neutral trial, there was no effect of ticagrelor compared with clopidogrel on reducing ALI. ALI is typically a thrombotic event: in TRA2°P-TIMI 50, the majority of ALI events were because of surgical graft thrombosis, followed by native vessel thrombosis, peripheral stent thrombosis, and a thromboembolic event.[21] Given

Table 3. Baseline Factors Associated With ALI Hospitalization Among the Overall Study Population

	HR (95% CI)	*P* Value
Age, per 10 y	0.8 (0.7, 1.0)	0.02
BMI, per unit increase, kg/m^2	1.0 (0.7–1.0)	0.03
Region (South America as the reference)		0.03
Asia	1.1 (0.5–2.1)	0.88
Europe	1.8 (1.0–3.2)	0.04
North America	1.7 (0.9–3.2)	0.08
Previous lower extremity revascularization	4.7 (3.3–6.8)	<.01
Previous atrial fibrillation	1.8 (1.1, 3.2)	0.03
Baseline ABI		<.01
Per 0.1 ABI decrease in patients with baseline ABI ≤0.60	1.3 (1.1–1.5)	<.01
Per 0.1 ABI decrease in patients with baseline ABI >0.60	1.1 (1.0–1.2)	0.16
Baseline statin use	0.7 (0.5–0.9)	<.01
Baseline angiotensin receptor blocker use	0.7 (0.5–1.0)	0.05
Randomized treatment: ticagrelor (clopidogrel as reference)	1.0 (0.8–1.3)	0.91

ABI indicates ankle-brachial index; BMI, body mass index; CI, confidence interval; and HR, hazard ratio.

Table 4. Subsequent Cardiovascular and Limb Events According to ALI Hospitalization

	ALI (n=232)	No ALI (n=13653)	All Randomized (n=13 885)
MACE (CV death/MI/ischemic stroke)	9.7	4.4	4.5
Before ALI	5.7		
After ALI	12.4		
MI	4.5	2.0	2.0
Before ALI	3.8		
After ALI	4.5		
Ischemic stroke	2.4	0.9	0.9
Before ALI	1.7		
After ALI	2.7		
CV death	4.7	2.0	2.0
All-cause mortality	7.7	3.6	3.6
Major amputation*	9.9	0.5	0.6
Before ALI	2.8		
After ALI	16.8		

All values represent exposure-adjusted event rate per 100 patient-years. ALI indicates acute limb ischemia; CV, cardiovascular; MACE, major adverse cardiovascular event; and MI, myocardial infarction.

*Major amputation includes lower extremity amputations at the level of or above the ankle.

this, a more intense antiplatelet therapy (ticagrelor) when compared with clopidogrel did not provide additional protection against ALI, whereas there is mechanistic plausibility for ALI prevention on a background of aspirin with rivaroxaban, a factor Xa inhibitor, and vorapaxar, a PAR-1 antagonist that inhibits thrombin-mediated platelet aggregation but may also have anticoagulant properties.[25]

Patients with symptomatic PAD in our study experienced ALI, which was associated with subsequent cardiac and limb events. Patients with ALI had a 14.2-fold greater risk of major amputation, which has been shown to be associated with significant morbidity, mortality, and cost.[26,27] We also observed a higher risk of all-cause mortality after ALI, as well as an immediate risk of post-ALI MACE. Notably, the risk of MACE continued to rise well beyond the initial acute limb event, likely reflecting the greater burden of comorbidities and severity of disease in patients with ALI. These results are consistent with previous reports of poor prognosis after ALI and major adverse limb events.[21,28]

The residual risk of acute ischemic limb events in this contemporary cohort of patients with symptomatic PAD highlights the need for effective strategies to prevent ALI. Consistent with the younger age of patients with versus without ALI, older age was associated with lower risk for ALI in our model. This may reflect survivor bias as well as lower use of revascularization procedures, which are associated with higher ALI risk, among older patients. In contrast, patients in our study with previous revascularization, atrial fibrillation, and more severe PAD, as evidenced by lower baseline ABI values, were at greater risk for ALI. Such patient characteristics could help providers identify these higher-risk individuals for whom more attention to thromboembolic prophylaxis for atrial fibrillation and more aggressive secondary prevention may be warranted. For example, in our study, statin use was associated with lower ALI risk, yet only 74% of patients in EUCLID were on baseline statin, compared with 82% statin use in TRA2°P-TIMI 50 and 90% use of lipid-lowering agents in COMPASS in the PAD subgroups. The lower use of statins observed in EUCLID may reflect the overall lower burden of coronary artery disease in our primary PAD population (29% vs. 53–57% and 68% in TRA2°P-TIMI 50 and COMPASS PAD subgroups, respectively), as data suggest that there is greater use of guideline-recommended therapies in patients with PAD with versus without concomitant coronary artery disease.[29] Observational studies have also demonstrated underuse of statins among primary PAD populations and have additionally shown that statin use is associated with lower risk of amputation.[30,31] Further support for the importance of lipid-lowering therapies in PAD comes from a subgroup analysis of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, which demonstrated significant reductions in ALI with the addition of evolocumab to a background of statin therapy.[23] In addition to ALI reduction strategies, better control of comorbid conditions, such as diabetes mellitus and hypertension, as well as smoking cessation

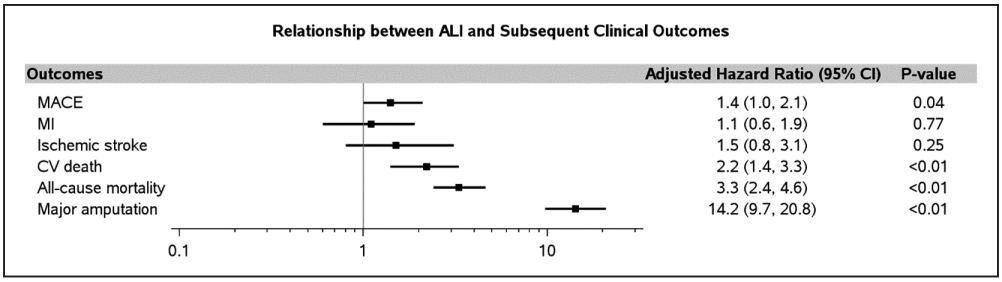

Figure 2. Relationship between ALI hospitalization and subsequent clinical outcomes.
Shown are hazard ratios and 95% confidence intervals (CI) for acute limb ischemia (ALI) hospitalization and each of the following clinical outcomes: major adverse cardiovascular events (MACE), myocardial infarction (MI), ischemic stroke, cardiovascular (CV) death, all-cause mortality, and major amputation.

counseling, are important to help lower risk of MACE overall and after an ALI event.

Future studies could also focus on modifiable factors, including revascularization techniques and postprocedural antithrombotic therapy, to mitigate the onset of and deleterious consequences associated with ALI. Among patients with previous revascularization in our study, surgical versus endovascular revascularization, particularly if performed more than 6 months prior, was associated with increased risk of ALI. Since surgical revascularizations are often performed in complex patients with extensive disease who may have exhausted endovascular options, the increased ALI risk associated with surgical revascularization may reflect a higher risk patient and/or higher procedural risk. However, combined with the fact that surgical graft thrombosis accounted for the majority of ALI events in the PAD subgroup of TRA°2P-TIMI 50,[21] these data also support investigation into better understanding and prevention of surgical graft failure; for example, through careful graft selection and analysis of distal run-off and further optimization of postrevascularization antithrombotic therapy, the latter of which is currently under investigation.[24] Closer patient monitoring and education to increase awareness among patients and non-vascular specialty providers regarding symptoms of ALI and the emergent nature of ALI are other strategies that could potentially reduce late ALI presentations for which amputation is the only treatment option.

Important strengths and limitations of this study should be acknowledged. This study examined a large primary PAD population and reported adjudicated ALI events in the context of a clinical trial that had low rates of lost-to-follow-up. However, this was a post hoc analysis. Although we were able to adjust for baseline characteristics, we could not adjust for postrandomization variables, and residual confounding likely exists. In addition, most patients in this study had claudication, and patients with peripheral revascularization within 30 days and those likely requiring revascularization or amputation within 3 months of randomization were excluded from EUCLID, limiting the generalizability of our results.

Conclusions

ALI is an important clinical event for patients with PAD. Risk factors associated with higher risk for ALI include any previous lower extremity revascularization, particularly surgical procedures more than 6 months prior, atrial fibrillation, and lower baseline ABI values, whereas older age and statin use are associated with lower risk of ALI. Hospitalization for ALI often portends poor prognosis and is associated with subsequent cardiovascular and limb events. Efforts to better understand and prevent ALI are needed.

ARTICLE INFORMATION

Received January 15, 2019; accepted July 2, 2019.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.039773.

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Acknowledgements

We thank Elizabeth Cook for her editorial contributions to this manuscript. Ms Cook did not receive compensation for her contributions apart from her employment at the institution where this study was conducted.

Sources of Funding

EUCLID was supported by AstraZeneca. The sponsor had no role in the conception or design of this analysis, interpretation of the data, or drafting of the manuscript.

Disclosures

Dr Hess reports receiving research funding from Merck and Bayer to CPC Clinical Research. Dr Patel reports receiving institutional research grants from

AstraZeneca, Bayer, HeartFlow, AHRQ, Janssen, Medtronic, and NHLBI; and consulting fees from AstraZeneca, Bayer, and Janssen. Dr Baumgartner reports receiving research grants from Abbott Vascular, Cook, Terumo, Amgen, and Boston Scientific; and consulting fees from Amgen. Dr Berger reports receiving advisory board fees from Janssen, Merck, and Takeda. Dr Blomster was an employee of AstraZeneca at the time of trial conduct. Dr Fowkes reports advisory boards for AstraZeneca, Merck, Bayer. Dr Held was an employee of AstraZeneca at the time of trial conduct. Dr Jones reports receiving research grants from Agency for Healthcare Research and Quality, AstraZeneca, American Heart Association, Bristol-Myers Squibb, Doris Duke Charitable Foundation, Patient-Centered Outcomes Research Institute; and honorarium/other from American College of Radiology, Daiichi Sankyo. Dr Katona is an employee of AstraZeneca. Dr Mahaffey reports receiving research grants from Afferent, Amgen, Apple Inc, AstraZeneca, CardivaMedical Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, NIH, Novartis, Sanofi, St. Jude, Tenax; and consulting fees from Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, Medergy, Medscape, Mitsubishi, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, SmartMedics, Springer Publishing, UCSF. Dr Norgren reports receiving research grants from AnGes, Mitsubishi; and steering committee honoraria from AnGes, AstraZeneca, Bayer, Cesca, Mitsubishi, Pluristem. Dr Rockhold reports receiving research funding from NIH, PCORI, Duke Clinical Research Institute, Astra Zeneca, ReNeuron, Luitpold, Alzheimer's Drug Discovery Foundation, Janssen, BMS; and equity interest in GlaxoSmithKline. Dr Hiatt reports receiving research funding from Bayer, AstraZeneca, Janssen, and NIH to CPC Clinical Research. The other authors report no conflicts.

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