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ORIGINAL INVESTIGATIONS

Cardiovascular Outcomes After Lower Extremity Endovascular or Surgical Revascularization

The EUCLID Trial

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ABSTRACT

BACKGROUND Lower extremity revascularization (LER) is a common treatment in patients with peripheral artery disease (PAD), but long-term outcomes are poorly defined.

OBJECTIVES The aim was to analyze LER in the EUCLID (Examining Use of tiCagreLor In paD) trial to determine predictors and cardiovascular outcomes.

METHODS Patients were grouped according to whether they received a post-randomization LER (n = 1,738) or not (n = 12,147). All variables were assessed for significance in univariable and parsimonious multivariable models. The primary endpoint was myocardial infarction, ischemic stroke, or cardiovascular death; major adverse limb events (MALE) included acute limb ischemia or major amputation.

RESULTS A post-randomization LER occurred in 12.5% of patients and was an endovascular LER in 74.7%. Endovascular LERs were performed more often in North America, whereas surgical procedures occurred more frequently in Europe. Independent factors predicting LER were prior and type of prior LER, geographic region, limb symptoms, diabetes, and smoking. A post-randomization LER was associated with an increased risk for the primary endpoint (hazard ratio: 1.60; 95% confidence interval: 1.35 to 1.90; $p < 0.0001$) and MALE (hazard ratio: 12.0; 95% confidence interval: 9.47 to 15.30; $p < 0.0001$). Event rates for the primary endpoint after LER were numerically higher in the surgical subgroup, but MALE were similar between surgical and endovascular LER.

CONCLUSIONS In the EUCLID trial, LER was most often endovascular. Following LER, there was an increased hazard for the primary endpoint (with higher event rates in the surgical group) and a markedly increased risk for MALE events (with similar event rates between surgical and endovascular LER procedures). (A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease [EUCLID]; NCT01732822)
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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ALI = acute limb ischemia

CI = confidence interval

HR = hazard ratio

LER = lower extremity revascularization

PAD = peripheral artery disease

TBI = toe-brachial index

Lower extremity peripheral artery disease (PAD) is a common cardiovascular disease affecting >200 million people worldwide (1). A contemporary review on the progression of PAD demonstrated that approximately 7% of asymptomatic patients with PAD progressed to intermittent claudication, and 21% of patients with initial intermittent claudication symptoms were diagnosed as having critical limb ischemia, with 4% to 27% undergoing major amputation within a mean follow-up of 6.3 years (2).

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A large and increasing number of patients with PAD are currently offered lower extremity revascularization (LER) with rapid development and availability of modern, minimally invasive endovascular revascularization techniques (3,4). This shift in clinical practice is presumably not related to a change in the patterns or natural history of PAD, but rather appears to be due to the continued evolution of technology available for endovascular treatment (5,6). In North America the total number of LER procedures performed almost doubled between 1996 and 2006, with endovascular interventions performed more commonly than bypass surgery. In parallel, there was a decrease in major lower extremity amputation by >25% (3). However, differences in clinical outcomes across treatment settings and geographic regions suggest that inconsistent use of LER exists (7).

Despite guidelines providing recommendations regarding LER, evidence for current practice is largely limited to comparative studies, nonrandomized cohorts, and regional or national databases (5,8). These guidelines provide guidance on treatment decisions mainly based on the complexity of the anatomical situation and, to a lesser extent, the clinical characteristics and prognostic factors of patients (5). Although LER is commonly performed in patients with symptomatic PAD, factors influencing the probability of LER and subsequent cardiac and limb outcomes after LER are poorly defined. In a subgroup analysis of the EUCLID (Examining Use of tiCagreLor In paD) trial, it was shown that patients with a prior LER before enrollment were at heightened risk for acute limb ischemia (ALI) requiring hospitalization and myocardial infarction compared with patients with symptomatic PAD enrolled on a low ankle-brachial index (ABI) without prior LER over a mean follow-up of 30 months (9).

This analysis describes the characteristics of patients who underwent post-randomization LER and identifies factors associated with LER and outcomes in patients enrolled in EUCLID. Type of intervention, either surgical or endovascular catheter-based lower limb procedures, and cardiovascular outcomes thereafter are described.

METHODS

The design and results of the EUCLID trial (NCT01732822) have been previously published (9–11). Briefly, EUCLID was an international, multicenter, double-blind trial that randomized 13,885 patients with symptomatic PAD to treatment with ticagrelor 90 mg twice daily or clopidogrel 75 mg daily. Eligible patients were ≥50 years of age with lower extremity PAD. Patients were enrolled with an abnormal ABI ≤0.80 at screening (n = 6,010) or a prior revascularization of the lower extremity >30 days prior to randomization (n = 7,875). Key exclusion criteria

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included planned use of dual antiplatelet therapy or the use of aspirin, high risk of bleeding, treatment with anticoagulation, poor metabolizer status for CYP2C19, planned revascularization (any territory), or major amputation within 3 months. All patients provided written informed consent, and institutional review boards at participating institutions approved the protocol. The overall results of the trial did not support superiority of ticagrelor over clopidogrel for the primary endpoint of a composite of myocardial infarction, ischemic stroke, or cardiovascular death (11).

The present post hoc analysis focuses on patients in the EUCLID trial who underwent post-randomization LER. In the EUCLID trial, data on LER, including type of revascularization and occurrence of the primary endpoint, ALI, major amputation, subsequent LER procedures, and Thrombolysis In Myocardial Infarction (TIMI) major bleeding, were systematically reported according to the trial design. Endpoints and hospitalizations for ALI (defined as clinical history of a symptomatic, rapid [within 7 days], or sudden decrease in limb perfusion requiring hospitalization, and either a new pulse deficit or confirmed arterial obstruction by imaging) were adjudicated by a clinical events classification group whose members were blinded to treatment assignment. Hospitalization for ALI was not considered a standard endpoint at the time of protocol development. However, the protocol was amended in December 2013 to collect source data for all hospitalizations for PAD, peripheral revascularization, and amputation. Trained adjudicators reviewed all information to determine whether patients had ALI defined as a hospitalization involving a rapid or sudden decrease in limb perfusion and 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. All patients in the EUCLID trial (n = 13,885) were grouped according to whether or not they had a post-randomization LER. Baseline characteristics were assessed for association with the outcome of LER using univariable and multivariable Cox models. Rates were computed as number of events per 100 patient-years (n/100 patient-years) of follow-up. Categorical variables are presented as counts (%) and continuous variables as median (25th, 75th percentile).

All baseline variables were first assessed for descriptive statistical significance in univariable Cox models. To determine the factors associated with post-randomization LER, a Cox proportional hazards model was fit with all baseline characteristics, including a further breakdown of the inclusion criteria to type of prior LER (surgical, endovascular, or both) and ABI/toe-brachial index (TBI) inclusion (as reference). Backward selection with a significance level of 0.10 for staying in the model was used to select the most important factors. Linearity assumptions were evaluated using flexible spline functions and linear piece-wise splines were created with a single interior knot at the inflection point when the assumption was violated. The proportional hazards assumption was assessed using Schoenfeld residuals; all variables in the model met this assumption. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for all factors in the parsimonious final model.

To compare the rates of the primary endpoint and limb events following LER to those without an LER, Cox models were fit with a time-dependent indicator for LER, taking a value of 1 after an LER occurring prior to censoring and 0 otherwise. Adjusted HRs and 95% CIs representing the risk of events following LER are presented. Event rates from randomization to the first LER, the event of interest, or censoring were computed, as well as event rates of subsequent revascularization, limb events, and the primary endpoint following the first post-randomization LER. Event rates after LER were also broken down within the 2 types of LER (surgical vs. endovascular). Rates were computed as n/100 patient-years of follow-up. Kaplan-Meier curves depicting the rates over time were created. Adjustment variables are shown in the Online Appendix.

RESULTS

A total of 1,738 patients (12.5%) enrolled in the EUCLID trial had post-randomization LER. Demographics of patients based on whether or not they had an LER are shown in **Table 1**. Patients undergoing post-randomization LER were more likely to smoke and to have diabetes, hypertension, hyperlipidemia, prior history of LER as inclusion criteria, and coexistent coronary and/or carotid artery disease. There was also a significant association with the geographic region of enrollment and LER with higher rates in North America and Europe and lower rates in Central/South America compared with Asia (**Table 1**).

The majority of patients with post-randomization LER had an endovascular intervention (n = 1,297 [74.7%]) that was most frequently performed in iliac (n = 389 [30.0%]) and superficial femoral arteries (n = 408 [31.5%]). In those with surgical procedures

TABLE 1 Baseline Characteristics of Patients With or Without a Post-Randomization LER

	LER Post-Randomization (n = 1,738)	No LER Post-Randomization (n = 12,147)	Univariate HR (95% CI)	p Value
Age, yrs*				<0.001
≥66	71 (68, 75)	72 (69, 77)	0.90 (0.85–0.95)	
<66	60 (57, 63)	60 (56, 63)	1.07 (1.01–1.14)	
Female	491 (28.3)	3,397 (28.0)	1.01 (0.91–1.13)	0.7840
BMI, kg/m^2	27 (24, 30)	27 (24, 30)	1.00 (0.99–1.01)	0.3920
Weight, kg*				0.005
≥76.5	89 (82, 97.5)	88 (82, 96)	1.04 (1.02–1.06)	
<76.5	66 (59.8, 72)	66 (59.6, 71.8)	0.98 (0.95–1.01)	
Region				<0.0001
Asia	150 (8.6)	1,452 (12.0)	0.83 (0.70–0.99)	
Central/South America	95 (5.5)	1,645 (13.5)	0.50 (0.40–0.62)	
Europe	862 (49.6)	6,636 (54.6)	Reference	
North America	631 (36.3)	2,414 (19.9)	1.89 (1.71–2.10)	
Randomized inclusion criteria				<0.0001
Prior revascularization	1,334 (76.8)	6,541 (53.8)	2.63 (2.35–2.94)	
ABI/TBI criteria	404 (23.2)	5,606 (46.2)	Reference	
Types of prior revascularization				<0.0001
Both endovascular and surgical	311 (17.9)	844 (7.0)	4.47 (3.86–5.18)	
Endovascular only	772 (44.4)	3,634 (29.9)	2.70 (1.39–3.04)	
Surgical only	242 (13.9)	1,962 (16.1)	1.65 (1.41–1.94)	
Neither†	413 (23.8)	5,706 (47.0)	Reference	
Limb symptoms (Rutherford)	1,387 (79.9)	9,894 (81.5)	1.08 (0.96–1.21)	0.2179
Major amputation	46 (2.7)	293 (2.4)	1.18 (0.88–1.58)	0.2704
Minor amputation	80 (4.6)	525 (4.3)	1.14 (0.91–1.43)	0.2397
Medical history				
Prior stroke/TIA/carotid stenosis or revascularization	507 (29.2)	2,935 (24.2)	1.28 (1.16–1.42)	<0.0001
Prior MI/CAD/coronary revascularization	594 (34.2)	3,438 (28.3)	1.30 (1.17–1.43)	<0.0001
Diabetes mellitus type I or II	721 (41.5)	4,624 (38.1)	1.16 (1.06–1.28)	0.0018
Hypertension	1,428 (82.2)	9,429 (77.6)	1.29 (1.14–1.46)	<0.0001
Hyperlipidemia	1,420 (81.7)	9,060 (74.6)	1.43 (1.27–1.62)	<0.0001
Current or former smoker	1,475 (85.5)	9,344 (77.4)	1.63 (1.43–1.87)	<0.0001
Number of vascular beds affected				<0.0001
1	870 (50.1)	6,934 (57.1)	Reference	
2	635 (36.5)	4,053 (33.4)	1.24 (1.12–1.37)	
3	233 (13.4)	1,160 (9.5)	1.57 (1.36–1.81)	
Medications before randomization				
Aspirin	1,272 (73.2)	7,999 (65.9)	1.38 (1.24–1.53)	<0.0001
Clopidogrel	740 (42.6)	3,733 (30.7)	1.62 (1.47–1.78)	<0.0001
DAPT	456 (26.2)	1,811 (14.9)	1.93 (1.73–2.15)	<0.0001
Statin	1,349 (77.6)	8,832 (72.7)	1.24 (1.11–1.39)	0.0001
ACE inhibitor	773 (44.5)	4,862 (40.0)	1.17 (1.07–1.29)	0.0009
Angiotensin-receptor blocker	442 (25.4)	3,046 (25.1)	1.01 (0.90–1.12)	0.8886
Cilostazol	238 (13.7)	1,857 (15.3)	0.91 (0.79–1.04)	0.1701
Randomized treatment				
Clopidogrel	892 (51.3)	6,063 (49.9)		
Ticagrelor	846 (48.7)	6,084 (50.1)		

Values are median (25th, 75th percentile) or n (%), unless otherwise indicated. Age is represented by 2 linear piece-wise splines with an inflection point at 66 years. Weight is represented by 2 linear piece-wise splines with an inflection point at 76.5 kg. p value is for the joint test. Major amputation is above the ankle. HRs are univariate and therefore unadjusted. *HR presented for a 5-U increase. †Includes other types of lower limb revascularization, such as mesenteric.

ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; LER = lower extremity revascularization; MI = myocardial infarction; TBI = toe-brachial index; TIA = transient ischemic attack.

(n = 440 [25.3%]), the most common were femoropopliteal bypass surgery (n = 179 [40.7%]) and common femoral artery endarterectomy (n = 121 [27.5%]) (Table 2).

Distribution of baseline characteristics by the post-randomization status of surgical (n = 440) or endovascular (n = 1,297) LER are shown in Table 3. Surgical bypass procedures were more commonly performed

TABLE 2 Post-Randomization LER by Type (First Incident) (N = 1,738)

Type of LER	
Endovascular	1,297 (74.7)
Surgical	440 (25.3)
Time to LER, days	358 (178, 609)
Type of surgical revascularization	
Aorto-bifemoral bypass	38/440 (8.6)
Axillary bifemoral bypass	11/440 (2.5)
Femoropopliteal bypass (above knee)	95/440 (21.6)
Femoropopliteal bypass (below knee)	84/440 (19.1)
Endarterectomy (common/superficial femoral artery)	121/440 (27.5)
Other	91/440 (20.7)
Location of endovascular revascularization	
Iliac	389/1,297 (30.0)
Superficial femoral artery	408/1,297 (31.5)
Popliteal	166/1,297 (12.8)
Common femoral artery	164/1,297 (12.6)
Tibial	46/1,297 (3.5)
Other	124/1,297 (9.6)

Values are n (%), median (25th, 75th percentile), or n/N (%).
LER = lower extremity revascularization.

TABLE 3 Baseline Characteristics of Patients Who Had a Surgical or Endovascular LER (First Event) After Randomization

	Post-Randomization LER	
	Surgical (n = 440)	Endovascular (n = 1,297)
Age, yrs	66 (60, 70)	66 (60, 72)
Female	100 (22.7)	391 (30.1)
Region		
Asia	40 (9.1)	110 (8.5)
Central/South America	37 (8.4)	58 (4.5)
Europe	260 (59.1)	601 (46.3)
North America	103 (23.4)	528 (40.7)
BMI, kg/m^2	26 (23, 30)	27 (24, 30)
Inclusion criteria for randomization		
Previous revascularization	304 (69.1)	1,029 (79.3)
ABI or TBI criteria	136 (30.9)	268 (20.7)
Limb symptoms at baseline	377 (85.7)	1009 (77.8)
Major amputation above the ankle	15 (3.4)	31 (2.4)
Medical history		
Prior stroke/TIA/carotid stenosis/ revascularization	118 (26.8)	389 (30.0)
Prior MI/CAD/coronary revascularization	125 (28.4)	469 (36.2)
Number of vascular beds affected		
1	249 (56.6)	620 (47.8)
2	139 (31.6)	496 (38.2)
3	52 (11.8)	181 (14.0)
Diabetes mellitus type I or II	172 (39.1)	548 (42.3)
Hypertension	354 (80.5)	1,073 (82.7)
Hyperlipidemia	333 (75.7)	1,086 (83.7)
Tobacco use		
Current	160 (36.4)	476 (37.0)
Former	213 (48.5)	626 (48.7)
Never	66 (15.0)	183 (14.2)
Medications before randomization		
Aspirin	284 (64.5)	988 (76.2)
Clopidogrel	164 (37.3)	575 (44.3)
DAPT	79 (18.0)	377 (29.1)
Statin	316 (71.8)	1,032 (79.6)
ACE inhibitor	192 (43.6)	581 (44.8)
Angiotensin receptor blocker	113 (25.7)	329 (25.4)

Values are median (25th, 75th percentile) or n (%).
BMI = body mass index; other abbreviations as in Table 1.

in patients from Central/South America and Europe, whereas endovascular procedures were more commonly performed in North America. Patients enrolled into the trial based on a history of a prior LER were more likely to have an endovascular LER post-randomization, whereas patients enrolled based on ABI/TBI criteria were more likely to undergo a surgical bypass post-randomization LER.

A history of LER prior to enrollment was most associated with post-randomization LER (Table 4). With that history, the highest risk was in patients who at baseline had a history of both surgical and endovascular revascularization (HR: 3.99; 95% CI: 3.42 to 4.66), followed by prior endovascular, and lowest risk for prior surgical bypass (HR: 1.65; 95% CI: 1.40 to 1.94). Additional factors associated with a post-randomization LER included region (North America: HR: 1.44; 95% CI:1.28 to 1.60), limb symptoms at baseline (HR: 1.32; 95% CI: 1.17 to 1.50), diabetes (HR: 1.28; 95% CI: 1.16 to 1.41), and current or former tobacco use (HR: 1.26; 95% CI: 1.09 to 1.45) (Table 4). Age ≥66 years was associated with a reduction in the risk of LER (HR: 0.91; 95% CI: 0.86 to 0.97 for every 5 year increase in age) (Table 4).

In patients experiencing a post-randomization LER, the risk for the primary endpoint was increased (HR: 1.60; 95% CI: 1.35 to 1.90) as was all-cause mortality (Table 5). Major adverse limb events (MALE) were greatly increased (HR: 12.0; 95% CI: 9.47 to 15.3), with similar increased risks for both ALI and major amputation. TIMI major bleeding was also increased in these patients (Table 5). The Central Illustration provides Kaplan-Meier estimates of the risk for the primary endpoint and MALE. These Central Illustration panels demonstrate an immediate increase in risk following the procedure that is most notable for MALE.

The rates remained elevated for both major cardiac and limb events, but were progressively higher compared with subjects who did not have a post-randomization LER. Table 6 provides descriptive

TABLE 4 Factors Associated With Post-Randomization LER—Parsimonious Multivariable Model

	HR (95% CI)	p Value
Age, yrs*		
Age ≥66	0.91 (0.86–0.97)	0.0017
Age <66	1.04 (0.98–1.11)	0.1836
Region (vs. Europe)		
North America	1.44 (1.28–1.60)	<0.0001
Central/South America	0.56 (0.45–0.70)	<0.0001
Asia	0.63 (0.52–0.76)	<0.0001
Weight, kg*		
<76.5	0.94 (0.91–0.97)	0.0006
≥76.5	1.00 (0.98–1.02)	0.8747
Type of prior revascularization (vs. neither)		
Both surgical and endovascular	3.99 (3.42–4.66)	<0.0001
Endovascular revascularization only	2.56 (2.25–2.92)	<0.0001
Surgical revascularization only	1.65 (1.40–1.94)	<0.0001
Limb symptoms	1.32 (1.17–1.50)	<0.0001
Prior TIA/stroke/carotid stenosis or revascularization	1.09 (0.98–1.22)	0.0953
Diabetes mellitus type I or II	1.28 (1.16–1.41)	<0.0001
Current or former smoker	1.26 (1.09–1.45)	0.0012

*HR represents risk for every 5-U change.
Abbreviations as in Table 1.

event rates (number/100 patient-years) for outcomes that occurred prior to the outcome event of interest in those who underwent a post-randomization LER compared with those who did not. Table 6 is further subdivided by endovascular and surgical procedures. In general, cardiac and limb events were numerically higher in patients undergoing surgical procedures, but surgical patients experienced fewer LERs after the index LER (Table 6). In addition, patients enrolled in the strata with a prior history of LER who underwent a post-randomization LER had higher event rates of the primary endpoint (8.1%) and ALI (5.0%). In contrast, the patients enrolled on ABI/TBI who had a post-randomization LER had lower rates for the primary endpoint (5.6%) and ALI (2.6%) following their LER.

TABLE 5 Risk of Primary Outcome, MALE, and Bleeding Events Following LER

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Primary outcome*†	1.77 (1.51–2.08)	<0.0001	1.60 (1.35–1.90)	<0.0001
All-cause mortality‡	1.46 (1.22–1.74)	<0.0001	1.38 (1.14–1.68)	0.0011
MALE§	14.4 (11.6–18.0)	<0.0001	12.0 (9.47–15.3)	<0.0001
ALI‖	17.2 (12.8–23.0)	<0.0001	13.9 (10.3–18.7)	<0.0001
Major amputation¶	13.3 (9.92–17.8)	<0.0001	10.6 (7.59–14.7)	<0.0001
TIMI major bleed#	3.08 (2.10–4.50)	<0.0001	2.77 (1.88–4.08)	<0.0001

HR obtained from Cox PH models with LER as a time-dependent variable. *Primary outcome = myocardial infarction, ischemic stroke, cardiovascular death. Models adjusted for: †Sex, inclusion criteria, region, Rutherford score, prior stroke, prior carotid revascularization, prior MI, prior PCI, prior CABG, diabetes, statin use, smoking status, major amputation, minor amputation, baseline ABI, age, weight, and GFR. ‡Sex, inclusion criteria, region, prior stroke, prior MI, diabetes, statins, ARB use, smoking status, major amputation, minor amputation, baseline ABI, age, weight, and baseline GFR. §Inclusion criteria, baseline Rutherford, prior carotid stenosis, prior carotid revascularization, diabetes, statin use, ARB, major amputation, minor amputation, and baseline ABI. ‖Inclusion criteria, prior carotid revascularization, statin use, ARB use, baseline ABI. ¶Inclusion criteria, carotid stenosis, carotid revascularization, baseline Rutherford, diabetes, statin use, major amputation, minor amputation, baseline ABI, and weight. #Inclusion criteria, region, sex, aspirin use, and age.

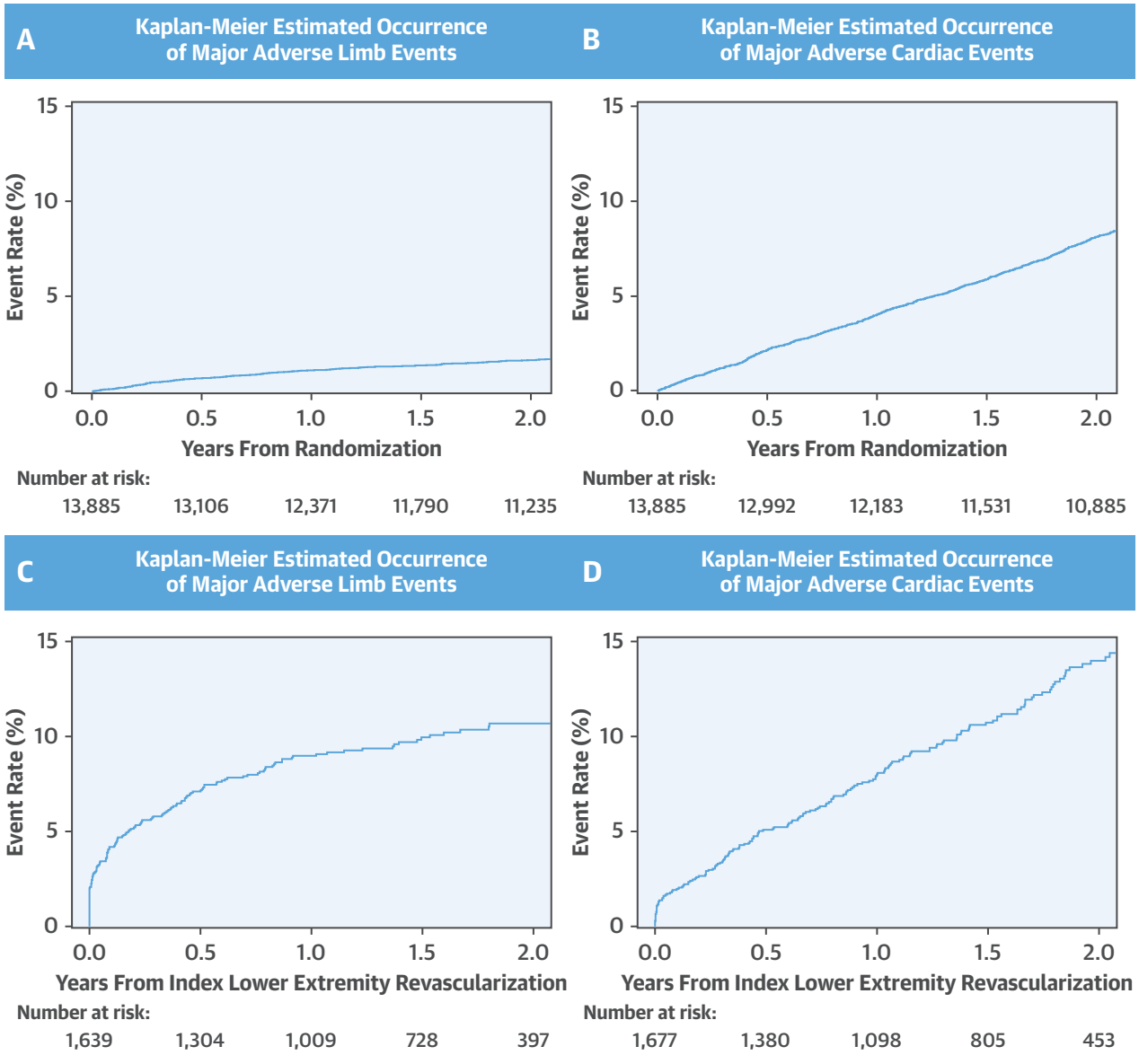
ALI = acute limb ischemia; MALE = major adverse limb event including acute limb ischemia or major amputation; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

DISCUSSION

This post hoc analysis provides insights on the characteristics and types of revascularization procedures occurring after randomization in the EUCLID trial (Central Illustration). Patients in EUCLID undergoing an index revascularization procedure after randomization (post-randomization LER) were more likely to have classical risk factors of smoking, diabetes, hypertension, hyperlipidemia, history of LER before enrollment, and involvement of multiple vascular beds compared with those who did not have a post-randomization LER. There was significant regional variation, with the highest number of patients with LER from North America followed by Europe, with endovascular procedures more commonly performed in North America and surgical procedures more commonly performed in Europe and Central/South America. This result is in accordance with findings from Goodney et al. (3) and others analyzing data from North America and Europe, showing that endovascular procedures increased >3-fold while the use of surgery decreased within the last 10 to 15 years (3,12). For differences in clinical practice with higher numbers of procedures in North America compared with the rest of the world, it is suggestive that reimbursement and logistic factors may contribute (13–15). However, further analysis on trends in procedure volume, relevance of regional factors in contrast to guideline-driven recommendations, and expenditures for PAD interventions are needed.

Independent factors associated with post-randomization LER indicated that the greatest risk was in patients who had a prior history of LER at baseline; this risk was graded and was highest in patients with a prior history of both surgical and endovascular procedures, lower in subjects with prior endovascular revascularization, and lowest in those with a prior surgical revascularization. In addition, factors associated with post-randomization LER that were statistically significant included the presence of limb symptoms, diabetes, current or former tobacco use, and geographic region of enrollment. Limb symptoms also predicted LER, which was reported by Klingelhoefer et al. (16), who described subjective improvement in symptoms as the most important prognostic factor for bypass function and limb

CENTRAL ILLUSTRATION **Kaplan-Meier Curves for Major Adverse Limb Events and Major Adverse Cardiac Events in Patients With and Without a Post-Randomization Lower Extremity Revascularization**



Baumgartner, I. et al. J Am Coll Cardiol. 2018;72(14):1563–72.

(A) Major adverse limb events (MALE) in patients who did not experience a post-randomization lower extremity revascularization. **(B)** Major adverse cardiac event (MACE) in patients who did not experience a post-randomization lower extremity revascularization. **(C)** MALE in patients who had a post-randomization lower extremity revascularization. **(D)** MACE in patients who had a post-randomization lower extremity revascularization. MALE was defined as the first event of major amputation or acute leg ischemia. MACE was defined as the first event of myocardial infarction, ischemic stroke, or cardiovascular death.

salvage without need for redo procedures. Diabetes and tobacco use, both of which independently increased the risk of LER by 25% in this analysis, are the most prevalent risk factors related to development and progression of PAD (17,18) and are well described as factors related to failure of LER and redo procedures (19-22), underlining the robustness of these findings. The result that a prior LER is an independent risk factor for post-randomization LER is in accordance with the findings from the recently published EUCLID subgroup analysis (9). This report demonstrated that patients with a history of prior

TABLE 6 Event Rates After Post-Randomization Lower Extremity Revascularization

	Rates (Event) of Outcomes Between Randomization and Occurrence of LER or End-of-Follow-Up (n = 13,885)	Rates (Event) for Subsequent Outcomes in Patients After LER* (n = 1,738)	Rates (Event) For Subsequent Outcomes in Patients After LER By LER Type	
			Endovascular LER	Surgical LER
Primary efficacy	4.25 (1,315)	7.55 (176)	7.23 (126)	8.50 (50)
All-cause death	3.48 (1,123)	5.52 (140)	4.63 (88)	8.19 (52)
MALE	0.77 (244)	7.20 (155)	5.42 (90)	13.29 (65)
Acute limb ischemia	0.42 (134)	4.41 (98)	3.55 (60)	7.16 (38)
Major amputation	0.41 (128)	3.70 (88)	2.49 (45)	7.61 (43)
Major bleeding	0.68 (189)	1.92 (33)	1.39 (18)	3.58 (15)

Values are event rates expressed as n/100 patient-years (number of events). *Events for subsequent outcomes were only counted if the event occurred after the LER. If an event occurred before the LER, then for that specific event, the patient is not used in calculating the subsequent outcome rate. The event rates represent the rates of the time-dependent models.

Abbreviations as in Tables 1 and 5.

LER had a heightened risk of subsequent myocardial infarction and ALI requiring hospitalization beyond other risk factors (9).

This post hoc EUCLID analysis provides temporal evidence that patients undergoing a post-randomization LER had an immediate increase in risk of the primary endpoint and all-cause mortality, but an even greater increase in risk for MALE. Whether these increased risks are directly related to the intervention, reflect a high-risk group, or both remains to be determined. Additional descriptive analyses demonstrated that patients enrolled in the strata with a prior history of LER accounted for three-quarters of the patients who underwent a post-randomization LER, and those patients had higher event rates for the primary endpoint and ALI than patients enrolled on ABI/TBI following their LER. This suggests that patients with a prior history of LER may represent a higher-risk population for subsequent revascularization procedures. However, quantifying these risks is informative in evaluating patients with PAD who are candidates for LER, particularly in terms of the risk for ALI and major amputation. A numeric description of these risks suggests higher cardiac risk and limb risk in patients undergoing a subsequent surgical LER; however, since surgical bypass is often reserved for more complex cases, these risks may indeed reflect the underlying severity of disease rather than the procedure.

In the published data, results from nonrandomized datasets remain contradictory, and most focus on critical limb ischemia (23). Agarwal et al. (12) compared cost utilization and in-hospital outcomes of endovascular and surgical revascularization procedures for critical limb ischemia and demonstrated that endovascular LER was associated with a significant lower rate of in-hospital death and major amputations in the United States from 2003 to 2011 (12). A meta-analysis of observational studies to assess the comparative effectiveness of endovascular and surgical LER in patients with critical limb ischemia by Jones et al. (24) showed a statistically nonsignificant reduction in all-cause mortality at 6 months and amputation-free survival at 1 year in patients treated with endovascular revascularization. However, there was no difference in overall death, amputation, or amputation-free survival at 2 years and beyond (24). Two propensity-score matched analyses on endovascular versus surgical LER gave contradictory results. Mehaffey et al. (25) merged data from the National Surgical Quality Improvement Program (propensity matching identified 1,924 patients per group) about treatment of patients with critical limb ischemia in the United States between 2011 and 2014. With multivariate logistic regression, bypass surgery with single-segment saphenous vein versus endovascular LER, bypass surgery with alternative conduit versus endovascular LER, antiplatelet therapy, and statin therapy were protective against MALE, whereas infrageniculate intervention and a history of prior bypass of the same arterial segment were predictive of MALE (25). In contrast, Wiseman et al. (26) evaluated amputation-free survival, overall survival, and relative rate of subsequent vascular intervention after endovascular or surgical LER in a propensity-score matched cohort (14,685 eligible patients, 5,928 endovascular and 5,928 open LER) of Medicare beneficiaries with PAD from 2006 to 2009. Patients undergoing endovascular LER had significantly improved amputation-free survival compared with open LER at 30 days; this benefit persisted at 4 years with 49% of endovascular patients versus 54%

of open LER patients having died or undergone major amputation. Using population-based data, it was demonstrated that endovascular LER is associated with improved amputation-free survival over the long term, with a modest relative increased risk of subsequent intervention (26).

STUDY LIMITATIONS. The EUCLID trial was not designed to specifically evaluate post-randomization LER. Potential unmeasured confounders of post hoc analyses require caution. Selection of vascular specialists following patients in the EUCLID trial might have influenced the clinically driven decision for LER. Although post-interventional antiplatelet and antithrombotic treatment might have influenced outcome, it was up to the decision of the operator. As treatment after revascularization was decided by the operator (except randomized treatment) and follow-up intervals following the index revascularization procedure after randomization were variable, no reliable statistical calculation could be done of the effectiveness of various medical regimens. The model did not look at competing risks, as those models are complex to interpret and there might have been confounders in the comparison of subtypes based on first occurrence. Finally, as endovascular LER has become the most common first intervention, it might be that open surgery is reserved for complex vascular situations with worse outcomes.

CONCLUSIONS

Statistical modeling demonstrated that a history of LER, the presence of limb symptoms, diabetes, current or former tobacco use, prior and type of prior LER, and living in North America are independently associated with LER. Major outcomes, including increased risk of the primary endpoint, cardiovascular death, ALI requiring hospitalization, and major amputation, were more frequent after a post-randomization LER.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with peripheral artery disease, a history of lower extremity revascularization is associated with a heightened risk of both cardiac and limb ischemic events and subsequent revascularization. The risk is greatest among those who have undergone both surgical and endovascular procedures.

TRANSLATIONAL OUTLOOK: Further studies are needed to explain the variation in risk related to geographical region of care and to develop treatment strategies that reduce the risk of recurrent ischemic events in this vulnerable population.

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KEY WORDS acute limb ischemia, cardiovascular event, diabetes, lower extremity revascularization, peripheral artery disease, smoking

APPENDIX For adjustment variables, please see the online version of this paper.