10.1161/CIRCULATIONAHA.116.025880

Ticagrelor Compared With Clopidogrel in Patients with Prior Lower Extremity Revascularization for Peripheral Artery Disease

Running title: Jones et al; Ticagrelor vs. Clopidogrel in Prior Revascularization for PAD

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Journal Subject Terms: Revascularization; Peripheral Vascular Disease

10.1161/CIRCULATIONAHA.116.025880

Abstract

***Background*—**In patients with symptomatic peripheral artery disease (PAD) with a history of limb revascularization, the optimal antithrombotic regimen for long-term management is unknown.

***Methods*—**The Examining Use of tiCagreLor In paD (EUCLID) trial randomized 13,885 patients with PAD to treatment with ticagrelor 90mg twice daily or clopidogrel 75mg daily. Patients were enrolled based on an abnormal ankle-brachial index (ABI) ≤0.80 or a prior lower extremity revascularization. This analysis focuses on the 7875 (57%) patients enrolled based on the prior lower extremity revascularization criterion. Patients could not be enrolled within 30 days of most recent revascularization, and patients with an indication for dual antiplatelet therapy were excluded. The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety endpoint was major bleeding.

***Results*—**Patients with a prior revascularization had a mean age of 66 years, 73% were male, and the median baseline ABI was 0.78. After adjustment for baseline characteristics, patients enrolled based on prior revascularization had similar rates of the primary composite endpoint (hazard ratio (HR) 1.10, 95% CI 0.98-1.23, p=0.12) and statistically significantly higher rates of myocardial infarction (HR 1.29, 95% CI 1.08-1.55, p=0.005) and acute limb ischemia (HR 4.23, 95% CI 2.86-6.25, p<0.001) when compared with patients enrolled based on ABI criteria. There were no differences in ticagrelor- versus clopidogrel-treated patients for the primary efficacy endpoint (11.4% vs. 11.3%; HR 1.01, 95% CI 0.88–1.15; p=0.90), all-cause mortality (9.2% vs. 9.2%; HR 0.99, 95% CI 0.86–1.15; p=0.93), acute limb ischemia (2.5% vs. 2.5%; HR 1.03, 95% CI 0.78–1.36; p=0.84), or major bleeding (1.9% vs. 1.8%; HR 1.15, 95% CI 0.83–1.59; p=0.41). The median duration of follow up was approximately 30 months.

***Conclusions*—**After adjustment for baseline characteristics, patients enrolled based on prior revascularization for PAD had higher rates of myocardial infarction and acute limb ischemia with similar composite rates of cardiovascular death, myocardial infarction, and stroke when compared with patients enrolled based on the ABI criterion. There were no significant differences between ticagrelor and clopidogrel for reduction of cardiovascular or acute limb events.

***Clinical Trial Registration*—**ClinicalTrials.gov (NCT01732822)

Key words: lower extremity revascularization; peripheral artery disease; ticagrelor

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Clinical Perspective

What is new?

- Patients with prior lower extremity revascularization had a heightened unadjusted risk of both cardiovascular and acute limb events when compared with patients who entered the study based on the ABI criterion.
- After adjustment for baseline characteristics, the risk of myocardial infarction and acute limb events remained statistically significantly higher while the risks of major adverse cardiovascular events and major bleeding were not statistically different in patients enrolled based on prior revascularization when compared with patients enrolled based on ABI criteria.

What are the clinical implications?

- Myocardial infarction and acute limb events were more common in patients enrolled based on prior revascularization when compared with patients enrolled based on ABI criteria.
- Ticagrelor did not reduce the primary composite endpoint of cardiovascular mortality, myocardial infarction, or ischemic stroke when compared with clopidogrel in patients with PAD and a history of lower extremity revascularization.

Peripheral artery disease (PAD) is considered a systemic manifestation of atherosclerosis that affects the arteries of the lower extremities, and is often thought to constitute a coronary heart disease risk equivalent due to the associated high cardiovascular morbidity and mortality.[1-4] Symptomatic patients most commonly present with either intermittent claudication or critical limb ischemia, and these are often the focus of treatment strategies to revascularize the limb.[5] Unlike patients with coronary artery disease (CAD), there is limited understanding of how to reduce the cardiovascular risk of patients with symptomatic PAD (whether treated with revascularization or medical therapy), and clinicians often rely on data from subgroup analyses of patients with PAD in antiplatelet and statin studies to guide cardiovascular risk reduction strategies.[6,7]

With limited proven medical therapies to reduce symptoms in patients with PAD, the use of peripheral endovascular and surgical revascularization for the symptomatic management of patients with PAD has increased dramatically over the past two decades.[8,9] When compared with revascularization for CAD, little evidence exists to guide clinicians on the choice and use of antiplatelet medications in patients with a history of peripheral revascularization procedures.[10] The optimal antithrombotic regimen for long-term management of patients with PAD after revascularization is poorly defined and often extrapolated from trials of patients undergoing percutaneous coronary intervention.

Two critical questions exist about the long-term prognosis and management of patients who have undergone prior lower extremity revascularization. First, are patients with prior revascularization at heightened risk for cardiovascular and limb events when compared with patients who have not undergone prior revascularization? Second, are more intensive antiplatelet medications more effective yet safe in this population? Ticagrelor is a potent $P2Y_{12}$ receptor

antagonist with evidence of benefit in patients with acute coronary syndromes and those with prior myocardial infarction.[11,12] The Examining Use of tiCagreLor In paD (EUCLID) trial was designed to evaluate treatment specifically in patients with PAD and tested the hypothesis that monotherapy with ticagrelor would be superior to clopidogrel in preventing cardiovascular endpoints in patients with PAD. This report describes the findings in the subgroup of patients who were enrolled based on a history of a prior lower extremity revascularization.

Methods

Study Design and Oversight

The design of EUCLID has been previously published.[13] Briefly, this was a double-blind, event-driven clinical trial that randomized 13,885 patients with PAD from 811 study sites in 28 countries. The trial was designed by an independent executive committee including members from the Duke Clinical Research Institute (DCRI; Durham, NC), Colorado Prevention Center at the University of Colorado School of Medicine (Aurora, CO), and AstraZeneca AB (Södertälje, Sweden), the trial sponsor. An international steering committee was also responsible for oversight of local study sites and included national lead investigators from each country. The DCRI managed the clinical database and conducted all analyses for publication independent of the sponsor. All primary efficacy and safety endpoints were adjudicated by an independent clinical events classification group who were blinded to treatment assignment. An independent data monitoring committee provided safety oversight.

Study Population

Eligible patients were ≥50 years of age with lower extremity PAD. These patients were enrolled with an abnormal ankle-brachial index (ABI) ≤0.80 at screening or a prior revascularization of

the lower extremity >30 days prior to randomization. The primary focus of this analysis is patients entering the study based on the prior revascularization criterion. Key exclusion criteria included planned use of dual antiplatelet therapy or the use of aspirin, a high risk of bleeding, or treatment with anticoagulation. All patients underwent genotype testing for CYP2C19, and those patients with a genotype with 2 loss-of-function alleles were excluded from the study. Planned need for revascularization (any territory) or major amputation within 3 months was also an exclusion criterion. All patients provided written informed consent and institutional review boards approved the protocols at participating institutions.

Data Collection

At baseline, sites collected and recorded general demographics and clinical characteristics and PAD-specific characteristics from patients in the electronic case report form (eCRF). Data regarding PAD symptom status were recorded and then categorized using the Rutherford and Fontaine classification systems. Additionally, investigators entered the date of and details regarding the most recent endovascular procedure (e.g., location of intervention) and surgical revascularization procedure (e.g., type of operation) in the eCRF. Finally, the level of prior amputation was recorded for all applicable patients.

Randomization and Study Treatment

Patients were randomized 1:1 to either ticagrelor 90 mg twice daily or clopidogrel 75 mg daily given in a double-blind fashion. At the time of randomization, patients were required to stop the use of open label aspirin and/or P_2Y12 inhibitors. Recruitment began in December 2012 and was completed in March 2014.

Endpoints

The primary efficacy endpoint was time from randomization to first occurrence of any event in

the composite of cardiovascular death, myocardial infarction, or ischemic stroke. Secondary endpoints included the primary composite endpoint plus acute limb ischemia, cardiovascular death alone, myocardial infarction, all-cause mortality, the primary composite endpoint including all-cause stroke, acute limb ischemia alone, time to lower extremity revascularization, and time to any revascularization. The primary safety endpoint was Thrombolysis in Myocardial Infarction (TIMI) major bleeding. The components of the primary efficacy endpoint, the primary safety endpoint, and all hospitalizations for acute limb ischemia were adjudicated by the independent clinical events classification group.

Hospitalization for acute limb ischemia 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 then reviewed all information to determine whether patients had acute limb ischemia defined as a hospitalization involving a rapid or sudden decrease in limb perfusion AND either (A) a new pulse deficit, rest pain, pallor, paresthesia, paralysis; OR (B) confirmation of arterial obstruction by limb hemodynamics (ankle or toe pressure) imaging, intra-operative findings, or pathological evaluation.

Statistical Analysis

The primary and secondary efficacy endpoints were analyzed using the intention-to-treat approach and were performed on the full analysis set consisting of all patients randomized to study drug irrespective of study drug adherence or withdrawal of consent. Patients who withdrew consent to participate in the study were included up to the date of their study termination with the exception of an analysis of all-cause mortality that used information from all patients for whom vital status could be determined via publically available records. The safety analyses were

performed on all patients who received at least 1 dose of study drug while on treatment, defined as within 7 days of the last dose of study drug.

The primary and secondary endpoints were analyzed in time-to-event analyses in a Cox proportional hazards model with a factor for treatment group. P-values and confidence intervals (CI) for the hazard ratios (HR) were based on the Wald statistic. Kaplan-Meier estimates of the cumulative proportion of patients with events were calculated and plotted.

Comparisons of event rates between patients enrolled based on ABI versus prior revascularization criteria were not pre-specified and were performed post hoc. P-values for differences between baseline characteristics (Table 1 and 2) were calculated using Chi-square (cell size ≥ 5) and Fisher's exact test (cell size < 5) for categorical variables and Wilcoxon's test for continuous variables. Adjusted analyses for the primary composite endpoint, components of the primary composite endpoint, ALI, and major bleeding (using baseline variables shown in Table 1) were performed to determine whether patients entering the study based on prior revascularization had higher rates of cardiovascular and acute limb events when compared with patients entering the study based on ABI criteria.

SAS version 9.4 was used for all analyses and all tests were two-sided.

Results

From December 2012 to March 2014, a total of 16,237 patients were enrolled and screened for randomization. After exclusion, 13,885 patients were randomized and followed for primary events until the primary analysis censoring date of May 9, 2016. A total of 7875 (57%) patients entered the study based on the prior lower extremity revascularization criterion. At the completion of the EUCLID study, a total of 14 patients did not have vital status known, of whom

5 were lost to follow up. The median length of follow up was approximately 30 months.

Baseline characteristics

Baseline characteristics by treatment assignment for patients who entered the study with a history of lower extremity revascularization are presented in **Table 1**. Patients had a mean age of 66 years, 73% were male, and the median baseline ABI was 0.78. When compared with patients enrolled on the ABI criterion, a lower proportion of patients enrolled based on prior revascularization were female (27.0% vs. 29.3%, p=0.004), while a higher proportion were from North America (28.6% vs. 13.2%, p<0.001), had carotid stenosis (19.0 vs. 15.3%, p<0.001), had undergone prior PCI or CABG (26.3% vs. 19.1%, p<0.001), and had vascular disease in >1 vascular bed (46.2% vs. 40.7%, p<0.001) (**Supplemental Table**). Patients with prior revascularization were more commonly current or former smokers, had a higher prevalence of lipid disorders, and a lower prevalence of diabetes mellitus. Patients with prior revascularization were also more commonly treated with cardioprotective medications including aspirin, clopidogrel, and statins prior to participation in the study, as compared with those enrolled based on the ABI criterion.

PAD-Specific and Prior Revascularization Characteristics

PAD-specific and prior revascularization baseline characteristics are presented in **Table 2**. At the time of enrolment, limb symptoms in patients with prior revascularization included intermittent claudication (64.0%) and critical limb ischemia (4.5%); 31.4% of patients were asymptomatic. In terms of most recent revascularization procedure prior to randomization, 63.5% of patients had endovascular revascularization and 36.3% had surgical revascularization. Notably, in 31.1% of patients the most recent revascularization procedure occurred between 30 days and 6 months prior to randomization, 31.4% between 6 months and 2 years prior to randomization, and 36.7%

>2 years prior to randomization. Additionally, 7.5% of patients with prior revascularization had previously undergone prior amputation (1.7% above knee amputation; 1.1% below knee amputation; 4.6% minor amputation including ankle disarticulation, foot and toe amputation) (**Supplemental Table 1**).

Event Rates in Prior Revascularization vs. ABI Groups

When compared with patients enrolled based on the ABI criterion, patients enrolled based on prior revascularization had higher rates of the primary composite endpoint (11.4% vs. 9.9%; HR 1.13, 95% CI 1.02–1.26; p=0.02), myocardial infarction (5.9% vs. 3.6%; HR 1.63 95% CI 1.38-1.91 p<0.001), acute limb ischemia (2.5% vs. 0.6%; HR 4.13, 95% CI 2.90–5.90; p<0.001), and TIMI major bleeding (1.8% vs. 1.3%; HR 1.41, 95% CI 1.07–1.85; p=0.01) (**Table 3**).

After adjustment for baseline variables, patients enrolled based on prior revascularization had non-statistically significantly higher rates of the primary composite endpoint (HR 1.10, 95% CI 0.98-1.23, p=0.12) but statistically significantly higher rates of MI (HR 1.29, 95% CI 1.08-1.55, p=0.005) and ALI (HR 4.23, 95% CI 2.86-6.25, p<0.001) when compared with patients enrolled based on ABI criteria (**Table 3**).

Efficacy Endpoint Based on Treatment Comparisons

In patients with a history of revascularization, the primary efficacy endpoint of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 11.4% of ticagrelor- versus 11.3% of clopidogrel-treated patients (HR 1.01, 95% CI 0.88–1.15; p=0.90) (**Figure 1**). The annualized event rate for acute limb ischemia was 1.01% in the ticagrelor group and 0.99% in the clopidogrel group. Other key secondary and composite endpoints including repeat revascularization were not different between treatment groups (**Table 4**).

Safety Endpoints Based on Treatment Comparisons

In patients with a history of revascularization, the primary safety endpoint, TIMI major bleeding, occurred in 1.9% of ticagrelor- versus 1.8% of clopidogrel-treated patients (HR 1.15, 95% CI 0.83–1.59; p=0.41) (**Figure 2**). Fatal bleeding, intracranial bleeding, and TIMI minor bleeding were all low frequency events and not different between treatment groups (**Table 5**).

There was no heterogeneity of treatment effects observed in those patients enrolled with versus without a history of limb revascularization (primary composite efficacy endpoint, $p_{interaction}$=0.72; primary safety endpoint, $p_{interaction}$=0.67). Additionally, when an on treatment analysis was performed in patients enrolled based on prior lower extremity revascularization, there were no significant differences in rates of the primary composite endpoint, components of the primary composite endpoint, or ALI between ticagrelor- and clopidogrel-treated patients.

Discussion

A primary finding of this subgroup was that the adjusted rates of MI and ALI were higher in patients enrolled based on prior lower extremity revascularization when compared with patients enrolled based on ABI criteria. Additionally, ticagrelor did not reduce the rate of major cardiovascular or acute limb endpoints when compared with clopidogrel in the overall population of patients with PAD in the EUCLID trial.[manuscript in press] This was also true in patients with PAD who entered the study based on the prior revascularization criterion. These findings suggest that patients with prior revascularization have a substantial residual rate of cardiovascular and acute limb events, despite high adherence to antiplatelet and statin medications, and require further study.

This study of patients with a history of limb revascularization is a representative cohort of

patients treated in contemporary clinical practice; 63.5% of patients had most recently undergone endovascular revascularization while 36.3% of patients had most recently undergone surgical revascularization. Because these patients met entry criteria based on the prior revascularization criterion, they were not required to be symptomatic (although 68.6% of patients reported symptoms at the time of enrollment). Notably, women were less likely to be enrolled based on prior lower extremity revascularization when compared with patients enrolled based on ABI criteria. Approximately one-third of patients who had undergone endovascular revascularization were most recently treated for disease of the iliac arteries and another one-third were treated for disease of the superficial femoral arteries, while the remaining patients had revascularization for disease of the common femoral, popliteal, and tibial arteries. Among patients with a history of limb revascularization, the most common surgical revascularization procedures prior to entering the trial were common or superficial femoral endarterectomy (6.0%), aorto-bifemoral bypass (5.7%), femoropopliteal (above knee) bypass (7.7%), and femoropopliteal (below knee) bypass (4.8%).

The current findings suggest that patients with a history of peripheral revascularization represent a cohort with a heightened risk of MI and ALI when compared with patients enrolled based on ABI criteria despite higher use of antiplatelet and statin drugs on entry. While the difference in risk of the primary composite endpoint was no longer statistically significant after adjustment for baseline factors, the critical question remaining is whether the medical community can determine treatment strategies to reduce risk and event rates in this population. To this point, there are few consensus statements available to guide clinicians in treating patients with PAD. Most of the empiric evidence has been derived from patients with stable PAD (i.e., not at the time of revascularization), including the CAPRIE subgroup analysis demonstrating a

reduction in cardiovascular events in patients with PAD taking clopidogrel as compared with aspirin.[6] Expert opinion regarding optimal antithrombotic medication use after revascularization has been extrapolated from literature developed in patients undergoing coronary revascularization procedures. The majority of the literature in PAD after endovascular revascularization was derived from studies of patients undergoing angioplasty alone and without sufficient information regarding disease burden and severity. Indeed, patients are currently being treated with advanced techniques including hybrid revascularization, trans-pedal access, and/or newer devices (e.g., atherectomy, drug-eluting stents, drug-coated balloons). It is clear that current invasive treatment approaches have outstretched the knowledge base for use of antiplatelet and concomitant medical therapies following revascularization.

While the EUCLID trial was not designed to specifically evaluate the use of ticagrelor after revascularization and there were no patients in EUCLID who were randomized while on dual antiplatelet therapy, this represents a large study of antiplatelet therapies in patients with PAD enrolled after revascularization procedures. As such, this subgroup analysis of the EUCLID trial has specifically focused on the long-term prevention of cardiovascular and acute limb events in this high-risk cohort of patients with a history of lower extremity revascularization. The results suggest that in patients with a history of revascularization (>30 days prior to enrollment) and for whom dual antiplatelet therapy was not required, antiplatelet inhibition with ticagrelor compared with clopidogrel does not provide additional benefit to reduce long-term cardiovascular and acute limb events.

The present findings not only add context to the current knowledge of antiplatelet monotherapy after revascularization for PAD, but they also highlight the need for more trials of antithrombotic agents after revascularization. Specifically, there is a lack of evidence about

whether patients should be treated with 1 or 2 antiplatelet agents, which agents should be used, duration of antiplatelet monotherapy or dual therapy, and whether antithrombotics that utilize different mechanistic pathways (e.g., $P2Y_{12}$ receptor antagonists, factor Xa inhibitors) should be used in isolation or in combination for these complex patients to reduce the long-term rates of cardiovascular events and acute limb ischemia. Finally, it is imperative to understand the impact of disease presentation, anatomic burden of disease, and type of revascularization procedures as the optimal antiplatelet medication regimen is being studied and developed.

There are limitations in this subgroup of patients with PAD who have undergone prior revascularization. First, all patients had to be >30 days from most recent revascularization procedure; thus no patients were enrolled immediately after revascularization. While an important evidence gap, 31.1% of patients were enrolled within 6 months of most recent revascularization, which constitutes an important potentially higher risk period for these patients with PAD. Second, despite the fact that this is a pre-specified subgroup analysis of the larger EUCLID trial, it is by far the largest cohort of patients with PAD and a history of revascularization enrolled to date in a clinical trial of antiplatelet medications. It is also important to note that patients deemed likely to require a new revascularization or amputation within 3 months were excluded from enrollment; thus the study population reflects clinically significant but stable PAD.

In conclusion, ticagrelor did not reduce the primary composite endpoint of cardiovascular mortality, myocardial infarction, or ischemic stroke when compared with clopidogrel in patients with PAD and a history of revascularization. After adjustment for baseline variables, the risk of MI and ALI remained statistically significantly higher while the risks of the primary composite endpoint and major bleeding were similar in patients enrolled based on prior revascularization

when compared with patients enrolled based on ABI criteria. While the EUCLID trial was not designed to singularly study the optimal antiplatelet medication regimen after lower extremity revascularization, the current findings highlight the need for future studies to better guide clinicians in treating patients post revascularization.

Acknowledgments: We thank Elizabeth Cook from the Duke Clinical Research Institute, who provided editorial assistance with the preparation the manuscript.

Funding Source: The EUCLID trial was supported by AstraZeneca.

Conflict of Interest Disclosures:

Jones: Institutional research grant from AstraZeneca.

Baumgartner: Research grants from Abbott Vascular, Cook, Optimed, Terumo, Promedics, Amgen, and Boston Scientific; Consulting fees from Astra Zeneca, Bayer, and Sanofi.

Hiatt: Institutional research grants from AstraZeneca, Bayer, Pleuristem, National Institutes of Health, and Kuyshu University Japan.

Heizer, Reist, White: Nothing to disclose

Conte: Consulting fees from Medtronic and Cook.

Berger: Institutional research grants from Astra Zeneca, National Heart, Lung, and Blood Institute, and American Heart Association; Consulting fees from Janssen, Merck, and Takeda.

Held, Katona, Blomster, Millegård: Employed by AstraZeneca

Mahaffey: Institutional research grants from Amgen, Daiichi, Johnson & Johnson, Medtronic, Merck, St. Jude, and Tenax; Consulting fees from AstraZeneca, American College of Cardiology, BAROnova, Bayer, Bio2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb, Cubist, Eli Lilly, Elsevier, Epson, Forest, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Mt. Sinai, Myokardia, Omthera, Portola, Purdue Pharma, Springer Publishing, The Medicines Company, Theravance, Vindico, and WebMD; Equity in BioPrint Fitness.

Norgren: Research grants from AnGes and Mitsubishi; Consulting fees from AstraZeneca, Bayer, AnGes, Pluristem, CESCA, and Mitsubishi.

Patel: Institutional research grants from AstraZeneca, CSL, HeartFlow, Janssen Research &

Development, Johnson & Johnson, Maquet, Medtronic, and National Heart, Lung, and Blood Institute; Consulting fees from Bayer Corporation, CSL, Genzyme, Janssen Research & Development, Medtronic, and Merck & Co.

Fowkes: Consulting fees from AstraZeneca, Bayer, and Merck.

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Table 1. Baseline characteristics of patients with prior revascularization according to treatment group

	Ticagrelor (n=3923)	Clopidogrel (n=3952)	p value
Age, median (25th, 75th), yrs	66.0 (60.0, 72.0)	66.0 (60.0, 72.0)	0.25
Female sex, no. (%)	1041 (26.5)	1088 (27.5)	0.32
Weight, median (25th, 75th), kg	76.0 (65.2, 88.0)	76.0 (65.6, 88.0)	0.58
Region, no. (%)			0.80
North America	1111 (28.3)	1139 (28.8)	
Europe	1921 (49.0)	1951 (49.4)	
Asia	593 (15.1)	569 (14.4)	
Central/South America	298 (7.6)	293 (7.4)	
Medical history, no. (%)			
History of stroke	338 (8.6)	325 (8.2)	0.53
History of TIA	164 (4.2)	145 (3.7)	0.24
History of carotid stenosis	751 (19.1)	748 (18.9)	0.80
Prior carotid revascularization	126 (3.2)	108 (2.7)	0.21
History of coronary artery disease**	1211 (30.9)	1233 (31.2)	0.76
Prior MI	673 (17.2)	715 (18.1)	0.28
Prior PCI or CABG	1046 (26.7)	1024 (25.9)	0.44
Number of vascular beds*			0.65
1	2119 (54.0)	2119 (53.6)	
2	1345 (34.3)	1389 (35.1)	
3	459 (11.7)	444 (11.2)	
Diabetes mellitus	1410 (35.9)	1424 (36.0)	0.94
Hypertension	3070 (78.3)	3102 (78.5)	0.82
Hyperlipidemia	3081 (78.5)	3125 (79.1)	0.57
Tobacco use, no. (%)			0.59
Never smoked	620 (15.8)	598 (15.1)	
Current smoker	1251 (31.9)	1296 (32.8)	
Former smoker	2017 (51.4)	2035 (51.5)	
Medications at baseline, no. (%)			
Aspirin	2885 (73.5)	2879 (72.8)	0.49
Clopidogrel	1571 (40.8)	1652 (41.8)	0.11
Statins	3007 (76.7)	3090 (78.2)	0.10
ACE inhibitor	1599 (40.8)	1573 (39.8)	0.39
Angiotensin receptor blocker	921 (23.5)	979 (24.8)	0.18
Cilostazol	588 (15.0)	589 (14.9)	0.92

*A vascular bed is defined as either PAD, prior CAD (prior MI, prior PCI, or prior CABG), or prior cerebrovascular disease (prior stroke, prior TIA, prior carotid artery stenosis or prior carotid revascularization).
**CAD is defined as if the patient either had a prior MI, prior PCI or prior CABG.

Table 2. PAD-specific baseline characteristics of patients with prior revascularization according to treatment group.

	Ticagrelor (N=3923)	Clopidogrel (N=3952)	p value
ABI values at baseline, median (25th, 75th)*	0.78 (0.62, 0.94)	0.78 (0.61, 0.94)	0.89
Type of most recent prior revascularization, no. (%)			0.42
Surgical	1443 (36.8)	1419 (35.9)	
Endovascular	2475 (63.1)	2528 (64.0)	
Time since most recent lower extremity revascularization			0.49
>30 days - ≤6 months	1197 (30.5)	1256 (31.8)	
>6 months - ≤2 years	1243 (31.7)	1226 (31.0)	
>2 years	1450 (37.0)	1442 (36.5)	
Location of prior endovascular revascularization, no. (%)			N/A
Iliac	1315 (33.5)	1359 (34.4)	
Common femoral artery	325 (8.3)	304 (7.7)	
Superficial femoral artery	1328 (33.9)	1351 (34.2)	
Popliteal	464 (11.8)	476 (12.0)	
Tibial	252 (6.4)	287 (7.3)	
Type of prior surgical revascularization, no. (%)			N/A
Endarterectomy (CFA/SFA)	387 (9.9)	407 (10.3)	
Aorto-bifemoral bypass	397 (10.1)	383 (9.7)	
Axillary bifemoral bypass	40 (1.0)	45 (1.1)	
Femoropopliteal bypass (above knee)	515 (13.1)	499 (12.6)	
Femoropopliteal bypass (below knee)	314 (8.0)	355 (9.0)	
Other	360 (9.2)	349 (8.8)	
Limb symptoms upon study entry, no. (%)†			0.80
Asymptomatic‡	1253 (31.9)	1223 (30.9)	
Mild/moderate claudication	1799 (45.9)	1850 (46.8)	
Severe claudication	695 (17.7)	702 (17.8)	
Rest pain	95 (2.4)	109 (2.8)	
Minor tissue loss (ischemic ulceration not exceeding ulcer of the digits of the foot)	60 (1.5)	57 (1.4)	
Major tissue loss (severe ischemic ulcers or frank gangrene)	20 (0.5)	10 (0.3)	
Prior amputation, no. (%)	300 (7.6)	291 (7.4)	0.07
Above knee amputation	58 (1.5)	79 (2.0)	
Below knee amputation	242 (6.2)	215 (5.4)	
Transtibial amputation	51 (1.3)	37 (0.9)	
Ankle disarticulation	4 (0.1)	3 (0.1)	
Partial foot amputation	26 (0.7)	25 (0.6)	
Toe amputation	161 (4.1)	147 (3.7)	

*ABI is calculated from site-reported measurements in the CRF, and is calculated as the average of enrollment and randomization ABI (or TBI) measurements, where at each visit, the lowest of the right and left ABIs (or TBIs) is selected.

†Using the Rutherford classification.

‡Symptom status at time of randomization (patients with a prior revascularization may have been asymptomatic at baseline).

Table 3. Unadjusted and adjusted event rates in patients enrolled based on a history of limb revascularization or abnormal ABI

	Inclusion Criteria		Unadjusted		Adjusted*	
	Prior revascularization (N=7875)	ABI (N=6010)	HR (95% CI)	P value	HR (95% CI)	P value
Primary efficacy outcome: CV death, myocardial infarction or ischemic stroke	894 (11.4%)	597 (9.9%)	1.13 (1.02, 1.26)	0.02	1.10 (0.98, 1.23)	0.12
Cardiovascular death	372 (4.7%)	334 (5.6%)	0.83 (0.72, 0.97)	0.02	0.97 (0.82, 1.14)	0.58
Myocardial infarction	466 (5.9%)	217 (3.6%)	1.63 (1.38, 1.91)	<0.001	1.29 (1.08, 1.55)	0.005
Ischemic stroke	176 (2.2%)	124 (2.1%)	1.06 (0.85, 1.34)	0.59	0.93 (0.72, 1.20)	0.58
Acute limb ischemia	196 (2.5%)	36 (0.6%)	4.13 (2.90, 5.90)	<0.001	4.23 (2.86, 6.25)	<0.001
TIMI major bleeding	143 (1.8%)	79 (1.3%)	1.41 (1.07, 1.85)	0.01	1.28 (0.94, 1.74)	0.12
Intracranial bleeding	44 (0.6%)	24 (0.4%)	1.42 (0.86, 2.33)	0.17	1.35 (0.76, 2.39)	0.30
Fatal bleeding	16 (0.2%)	14 (0.2%)	0.89 (0.43, 1.81)	0.74	1.22 (0.54, 2.78)	0.63

* Risk adjusted for all variables in Table 1: age, sex, weight, region, medical history, tobacco use, and medications at baseline

Table 4. Efficacy endpoints for patients with prior revascularization according to treatment group.

	Ticagrelor (N=3923)	Clopidogrel (N=3952)	HR (95% CI)	P value
Primary outcome: Composite of CV death, MI, or ischemic stroke	447 (11.4%)	447 (11.3%)	1.01 (0.88–1.15)	0.898
Event rate, %/100 pt-yrs	4.67 (4.26, 5.12)	4.63 (4.22, 5.08)		
CV death	190 (4.8%)	182 (4.6%)	1.05 (0.86–1.29)	0.634
Event rate, %/100 pt-yrs	1.91 (1.65, 2.20)	1.81 (1.57, 2.10)		
MI	237 (6.0%)	229 (5.8%)	1.05 (0.87–1.25)	0.629
Event rate, %/100 pt-yrs	2.46 (2.16, 2.79)	2.35 (2.07, 2.68)		
Ischemic stroke	76 (1.9%)	100 (2.5%)	0.76 (0.57–1.03)	0.078
Event rate, %/100 pt-yrs	0.77 (0.62, 0.97)	1.01 (0.83, 1.23)		
Key secondary efficacy outcome: Composite of CV death, MI, ischemic stroke, and ALI requiring hospitalization	522 (13.3%)	529 (13.4%)	1.00 (0.88–1.12)	0.947
Other secondary outcomes				
All-cause mortality	359 (9.2%)	364 (9.2%)	0.99 (0.86–1.15)	0.925
Composite of CV death, MI, or all-cause stroke	456 (11.6%)	461 (11.7%)	1.00 (0.88–1.14)	0.970
ALI	99 (2.5%)	97 (2.5%)	1.03 (0.78–1.36)	0.835
Event rate, %/100 pt-yrs	1.01 (0.83, 1.24)	0.99 (0.81, 1.20)		
Lower extremity revascularization	654 (16.7%)	680 (17.2%)	0.97 (0.87–1.07)	0.519
Composite of all revascularization (coronary and peripheral [limb, mesenteric, renal, carotid, and other])	906 (23.1%)	914 (23.1%)	1.00 (0.91–1.09)	0.929

Data presented as no. (%), unless otherwise indicated.

Table 5. Safety endpoints for patients with prior revascularization according to treatment group (on-treatment population).

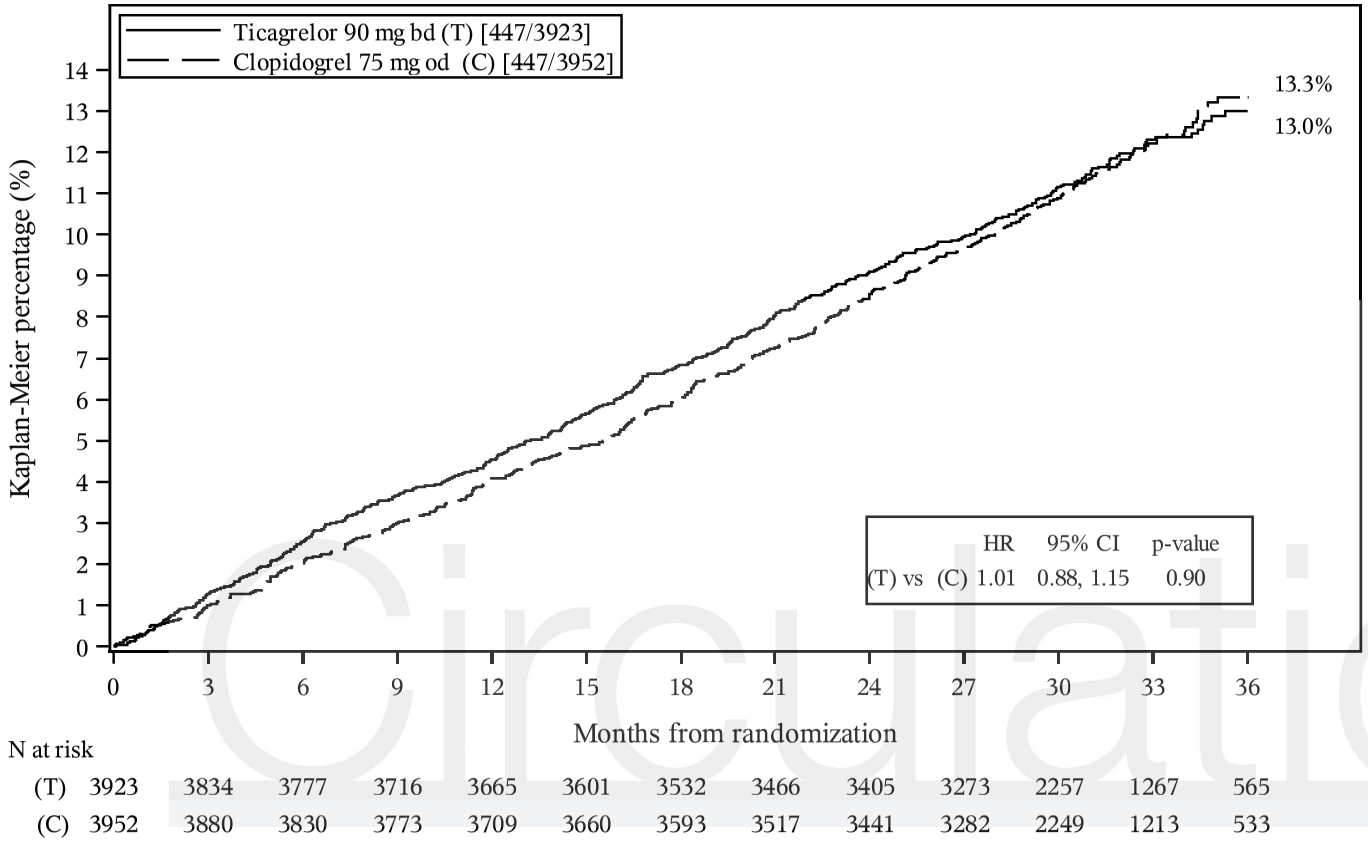
	Ticagrelor (N=3911)	Clopidogrel (N=3938)	HR (95% CI)	P value
Primary safety outcome: TIMI major bleeding	74 (1.9%)	69 (1.8%)	1.15 (0.83–1.59)	0.413
Intracranial bleeding	22 (0.6%)	22 (0.6%)	1.06 (0.59–1.92)	0.840
Fatal bleeding	5 (0.1%)	11 (0.3%)	0.49 (0.17–1.40)	0.180
TIMI minor bleeding	62 (1.6%)	51 (1.3%)	1.30 (0.89–1.88)	0.171

Figure Legends:

Figure 1. Kaplan-Meier plot of primary efficacy outcome (composite of CV death, MI, or ischemic stroke).

Figure 2. Kaplan-Meier plot of primary safety outcome (TIMI major bleeding).

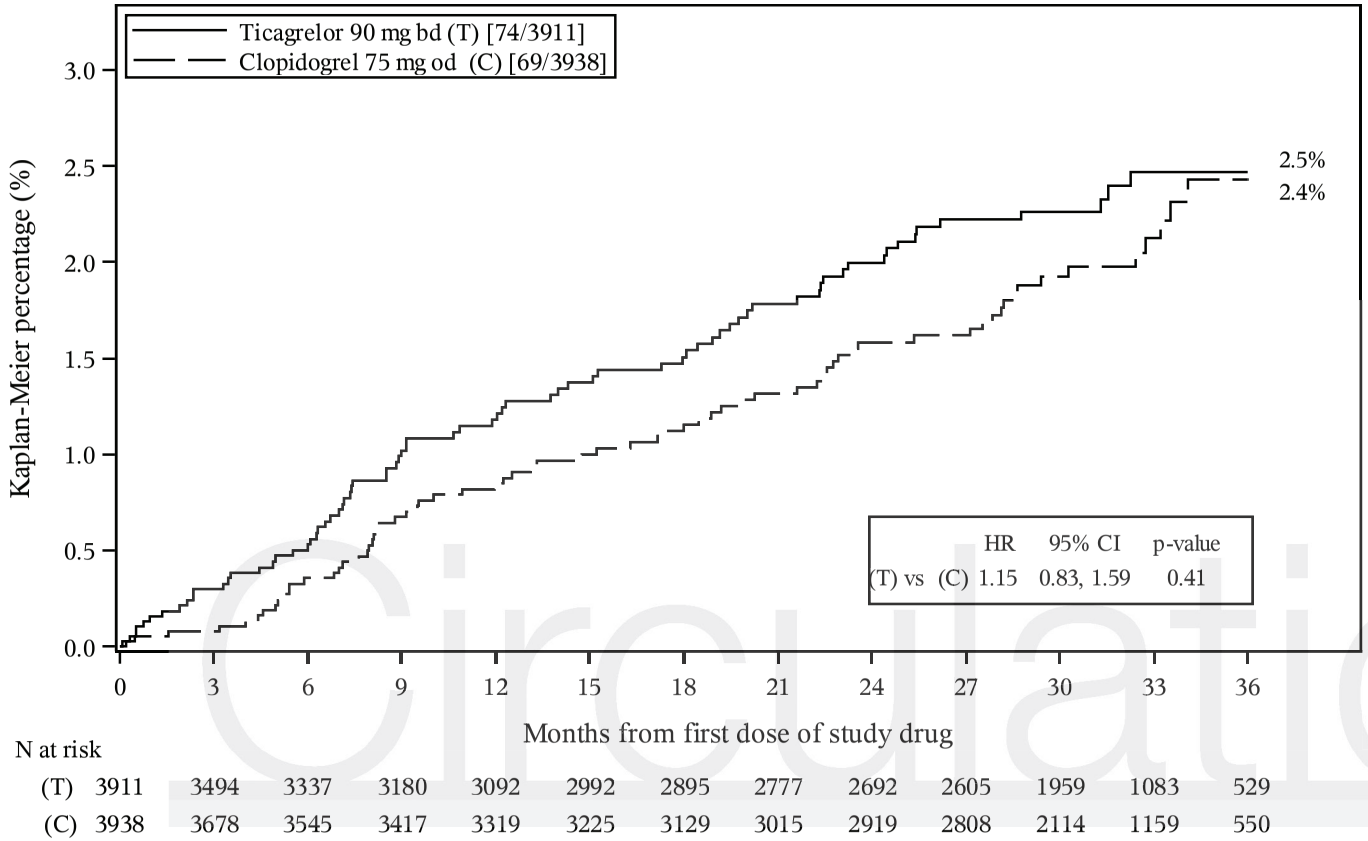
Ticagrelor Study D5135C00001 (EUCLID)



N at risk

(T)	3923	3834	3777	3716	3665	3601	3532	3466	3405	3273	2257	1267	565
(C)	3952	3880	3830	3773	3709	3660	3593	3517	3441	3282	2249	1213	533

Ticagrelor Study D5135C00001 (EUCLID)



N at risk

(T)	3911	3494	3337	3180	3092	2992	2895	2777	2692	2605	1959	1083	529
(C)	3938	3678	3545	3417	3319	3225	3129	3015	2919	2808	2114	1159	550

Ticagrelor Compared With Clopidogrel in Patients with Prior Lower Extremity Revascularization for Peripheral Artery Disease

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Circulation. published online November 13, 2016;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Supplemental Material

Supplemental Table 1. Baseline characteristics and PAD characteristics of patients enrolled based on prior lower extremity revascularization when compared with ABI criteria

	Enrolled Based on Prior Revascularization (N=7875)	**Enrolled Based on ABI (N=6010)**	**P value**	**Total EUCLID Population (N=13885)**
Age, median (25th, 75th), yrs	66.0 (60.0,72.0)	66.0 (61.0,73.0)	<.001	66.0 (60.0,73.0)
Female sex, no. (%)	2129 (27.0)	1759 (29.3)	0.004	3888 (28.0)
Weight, median (25th, 75th), kg	76.0 (65.5, 88.0)	77.0 (67.0, 88.0)	0.047	76.5 (66.0, 88.0)
Region, no. (%)			<.001	
North America	2250 (28.6)	795 (13.2)		3045 (21.9)
Europe	3872 (49.2)	3626 (60.3)		7498 (54.0)
Asia	1162 (14.8)	440 (7.3)		1602 (11.5)
Central/South America	591 (7.5)	1149 (19.1)		1740 (12.5)
PAD history				
ABI values at baseline, median (25th, 75th)[*]	0.78 (0.61, 0.94)	0.65 (0.54, 0.73)	<.001	0.70 (0.58, 0.82)
Type of prior revascularization, no. (%)			0.037	
Surgical	2862 (36.3)	24 (0.4)[§§]		2886 (20.8)
Endovascular	5003 (63.5)	23 (0.4)[§§]		5026 (36.2)
Time since most recent lower extremity revascularization			NA	

	Enrolled Based on Prior Revascularization (N=7875)	Enrolled Based on ABI (N=6010)	P value	Total EUCLID Population (N=13885)
>30 days - ≤6 months	2453 (31.1)	3 (0.0)		2456 (17.7)
>6 months - ≤2 years	2469 (31.4)	15 (0.2)		2484 (17.9)
>2 years	2892 (36.7)	29 (0.5)		2921 (21.0)
Type of prior surgical revascularization, no. (%)			NA	3495 (25.2)
Endarterectomy (CFA/SFA)	794 (10.1)	17 (0.3)		811 (5.8)
Aorto-bifemoral bypass	780 (9.9)	37 (0.6)		817 (5.9)
Axillary bifemoral bypass	85 (1.1)	4 (0.1)		89 (0.6)
Femoropopliteal bypass (above knee)	1014 (12.9)	22 (0.4)		1036 (7.5)
Femoropopliteal bypass (below knee)	669 (8.5)	36 (0.6)		705 (5.1)
Other	709 (9.0)	35 (0.6)		744 (5.4)
Limb symptoms upon study entry, no. (%)†			<.001	
Asymptomatic‡	2476 (31.4)	125 (2.1)		2601 (18.7)
Mild/moderate claudication	3649 (46.3)	3761 (62.6)		7410 (53.4)
Severe claudication	1397 (17.7)	1831 (30.5)		3228 (23.2)
Rest pain	204 (2.6)	174 (2.9)		378 (2.7)

	Enrolled Based on Prior Revascularization (N=7875)	Enrolled Based on ABI (N=6010)	P value	Total EUCLID Population (N=13885)
Minor tissue loss (ischemic ulceration not exceeding ulcer of the digits of the foot)	117 (1.5)	90 (1.5)		207 (1.5)
Major tissue loss (severe ischemic ulcers or frank gangrene)	30 (0.4)	28 (0.5)		58 (0.4)
Prior amputation, no. (%)	591 (7.5)	330 (5.5)	<.001	921 (6.6)
Above knee amputation	137 (1.7)	65 (1.1)		202 (1.5)
Below knee amputation	454 (5.8)	265 (4.4)		719 (5.2)
Transtibial amputation	88 (1.1)	49 (0.8)		137 (1.0)
Ankle disarticulation	7 (0.1)	3 (0.0)		10 (0.1)
Partial foot amputation	51 (0.6)	38 (0.6)		89 (0.6)
Toe amputation	308 (3.9)	175 (2.9)		483 (3.5)
Medical history, no. (%)				
History of stroke	663 (8.4)	480 (8.0)	0.358	1143 (8.2)
History of TIA	309 (3.9)	198 (3.3)	0.050	507 (3.7)
History of carotid stenosis	1499 (19.0)	922 (15.3)	<.001	2421 (17.4)
History of coronary artery disease	2444 (31.0)	1588 (26.4)	<0.001	4032 (29.0)
Prior MI	1388 (17.6)	1134 (18.9)	0.060	2522 (18.2)
Prior PCI or CABG	2070 (26.3)	1149 (19.1)	<.001	3219 (23.2)

	Enrolled Based on Prior Revascularization (N=7875)	Enrolled Based on ABI (N=6010)	P value	Total EUCLID Population (N=13885)
Number of vascular beds§			<.001	
1	4238 (53.8)	3566 (59.3)		7804 (56.2)
2	2734 (34.7)	1954 (32.5)		4688 (33.8)
3	903 (11.5)	490 (8.2)		1393 (10.0)
Diabetes mellitus	2834 (36.0)	2511 (41.8)	<.001	5345 (38.5)
Hypertension	6172 (78.4)	4685 (78.0)	0.554	10857 (78.2)
Hyperlipidemia	6206 (78.8)	4274 (71.1)	<.001	10480 (75.5)
Tobacco use, no. (%)			<.001	
Never smoked	1218 (15.5)	1766 (29.4)		2984 (21.5)
Current smoker	2547 (32.3)	1742 (29.0)		4289 (30.9)
Former smoker	4052 (51.5)	2478 (41.2)		6530 (47.0)
Medications at baseline, no. (%)				
Aspirin	5764 (73.2)	3507 (58.4)	<.001	9271 (66.8)
Clopidogrel	3223 (40.9)	1250 (20.8)	<.001	4473 (32.2)
Statins	6097 (77.4)	4084 (67.9)	<.001	10181 (73.3)
ACE inhibitor	3172 (40.3)	2463 (41.0)	0.404	5635 (40.6)
Angiotensin receptor blocker	1900 (24.1)	1588 (26.4)	0.002	3488 (25.1)
Cilostazol	1177 (14.9)	918 (15.3)	0.592	2095 (15.1)

*ABI is calculated from site-reported measurements in the CRF, and is calculated as the average of enrollment and randomization ABI (or TBI) measurements, where at each visit, the lowest of the right and left ABIs (or TBIs) is selected.
†Using the Rutherford classification.
‡Symptom status at time of randomization (patients with a prior revascularization may have been asymptomatic at baseline).

[§]A vascular bed is defined as either PAD, prior CAD (prior MI, prior PCI, or prior CABG), or prior cerebrovascular disease (prior stroke, prior TIA, prior carotid artery stenosis or prior carotid revascularization).
[§§] Some patients enrolled based on ABI criteria were later noted to have undergone prior revascularization. Since they were enrolled based on this criterion, they were analyzed as part of this group.

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