Eur J Vasc Endovasc Surg (2018) 55, 109–117

Outcomes of Patients with Critical Limb Ischaemia in the EUCLID Trial☆

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WHAT THIS PAPER ADDS

EUCLID was the first large trial to study the effect of antiplatelet treatment (ticagrelor versus clopidogrel) in patients with peripheral artery disease. Demographics, medical history, and outcomes for the subgroup of patients with critical limb ischaemia are presented. The study adds important epidemiological information about this patient group in a contemporary setting of antithrombotic treatment.

Objectives: Critical limb ischaemia (CLI) implies an increased risk of cardiovascular morbidity and mortality, and the optimal antithrombotic treatment is not established.

Design, Materials, Methods: The EUCLID trial investigated the effect of monotherapy with ticagrelor versus clopidogrel in 13,885 patients with peripheral artery disease (PAD); the primary endpoint was cardiovascular death, myocardial infarction, or ischaemic stroke. Patients planned for revascularisation or amputation within 3 months, were excluded. This analysis focuses on the subgroup with CLI, defined by rest pain (58.8%), major (9.0%) or minor (32.2%) tissue loss.

Results: In EUCLID, 643 patients (4.6%) had CLI at baseline. Diabetes mellitus was more common in the CLI group, while coronary disease, carotid disease, and hypertension were more common in the non-CLI group. A majority of CLI patients (62.1%) had only lower extremity PAD. In patients enrolled on the ankle brachial index (ABI) criteria, ABI was 0.55 ± 0.21 (mean ± SD) for those with CLI versus 0.63 ± 0.15 for those without CLI. The primary efficacy endpoint significantly increased among patients with CLI compared with those without CLI with a rate of 8.85 versus 4.28/100 patient years (adjusted for baseline characteristics hazard ratio [HR] 1.43 [95% CI 1.16–1.76]; $p = 0.0009$). When acute limb ischaemia requiring hospitalisation was added to the model, significant differences remained (adjusted HR 1.38, [95% CI 1.13–1.69]; $p = 0.0016$). The 1 year mortality was 8.9%. A trend towards increased lower limb revascularisation among those with CLI was observed. Bleeding (TIMI major, fatal, intracranial) did not differ between those with and without CLI.

Conclusions: Nearly 5% of patients enrolled in EUCLID had CLI at baseline. Milder forms of CLI dominated, a result of the trial design. Patients with CLI had a significantly higher rate of cardiovascular mortality and morbidity versus those without CLI. Further efforts are required to reduce the risk of cardiovascular events in PAD, especially in patients with CLI.

ClinicalTrials.gov: NCT01732822.

Article history: Received 17 August 2017, Accepted 7 November 2017, Available online 20 December 2017

Keywords: Critical limb ischaemia, Demographics, Medical history, Antithrombotic treatment, Trial data

INTRODUCTION

Critical limb ischaemia (CLI), defined by ischaemic rest pain or ischaemic wounds and necrosis and proven arterial occlusive disease,[1] affects 1–3% of all patients with peripheral artery disease (PAD).[2] In the United States, a CLI prevalence of 1.3% has been reported,[3] and it is generally calculated that 500–1000 new cases per million appear

☆ EUCLID was sponsored by AstraZeneca.

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https://doi.org/10.1016/j.ejvs.2017.11.006

annually.[1] The outcome is extremely serious, including an historical 1 year mortality up to 25% and a major amputation risk of 20—30%.[3] More recent experience from a clinical trial in patients with CLI unsuitable for lower extremity revascularisation[4] showed a 1 year all cause mortality rate of 16%, of which over half the deaths were non-cardiovascular or of unknown cause. The annual risk of major amputation was approximately 23%.

CLI is almost exclusively a manifestation of atherosclerosis, and as in all PAD there is an association with atherosclerosis in coronary and carotid territories.[5,6] A considerable proportion of patients with CLI also have diabetes mellitus, a particularly strong risk factor for PAD overall.[7] Occlusions and stenoses in CLI are commonly multifocal and located from the femoral to the tibial arteries, less frequently proximal to the groin but predominantly distally. The single guideline recommendation for treatment of limb symptoms and to prevent major amputation in CLI is revascularisation.[1,8] The atherothrombotic aetiology[9] makes it reasonable to assume that CLI implies a substantial thrombotic risk,[10] based on a higher level of platelet and monocyte activation.[11] A revascularisation procedure also enhances the risk of a thrombotic process.[12,13] The need for an antithrombotic treatment is therefore well established, and antiplatelet medication is the first choice.

Ticagrelor, a reversible direct P2Y12 inhibitor, was shown to reduce major cardiovascular events in patients on aspirin with acute coronary syndrome compared with clopidogrel in the PLATO (Platelet Inhibition and Patient Outcome) study.[14] In the PEGASUS-TIMI 54 (Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54) trial[15] that included patients on aspirin with a history of myocardial infarction and concomitant PAD, ticagrelor significantly reduced major adverse cardiovascular events (MACE) and major adverse limb events (MALE).

The EUCLID (Examining Use of Ticagrelor In Peripheral Artery Disease) trial (NCT01732822) was designed to compare monotherapy with ticagrelor or clopidogrel in patients with PAD.

METHODS

EUCLID was a prospective, multicentre, randomised, double blind, event driven study. It was approved by institutional review committees of participating institutions and national ethics committees, as appropriate. All patients gave written informed consent. The details of the trial design[16] and results[17] have been published previously. Patients were enrolled with symptomatic PAD, defined as typical intermittent claudication or other leg discomfort associated with physical limitations from PAD, or symptoms of CLI and an ankle brachial index (ABI) $\leq$0.80 (at the second visit before inclusion an ABI $\leq$0.85 was accepted). When the ABI was $>$1.40, a toe brachial index (TBI) of $\leq$0.60 was required. Patients with a prior history of a lower limb revascularisation were enrolled regardless of their baseline ABI. Patients homozygous for the cytochrome P-450 2C19 allele (3.8%) were not included. EUCLID compared monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily) in patients $>$50 years of age who were followed for a median of 30 months. The study included 13,885 patients, 56.7% with a prior revascularisation performed more than 30 days before enrollment, and 43.3% with an abnormal ABI. The primary efficacy endpoint was time to first event in the composite of cardiovascular death, myocardial infarction, or ischaemic stroke. In the overall trial results, ticagrelor was not superior to clopidogrel for the reduction of cardiovascular events (HR 1.02 (95% CI 0.92—1.13), $p = 0.65$), and major bleeding did not differ between the treatments (HR 1.10 (95% CI 0.84—1.43), $p = 0.49$).[17]

The present analysis focuses on patients in EUCLID with CLI at baseline, considered to carry the highest risk for thrombotic events. CLI was defined clinically by ischaemic rest pain, ischaemic ulcers, or gangrene. There were no predefined ABI or TBI criteria specifically defining CLI.

The aim of this substudy was to investigate the demographic differences, medical history, and risk of outcome events between patients with and without CLI. The primary efficacy and safety endpoints corresponded to those of the main EUCLID study: time to first occurrence of any event in the composite of cardiovascular death, myocardial infarction, or ischaemic stroke and thrombolysis in myocardial infarction (TIMI) major bleeding, respectively. Secondary endpoints included all cause mortality, cardiovascular and non-cardiovascular death, hospitalisation for acute limb ischaemia (ALI), lower limb revascularisation, any revascularisation, and major and minor amputation. As this was a subgroup analysis, there was no sample size or power calculation.

Statistics

Continuous variables were summarised as median with 25th and 75th percentiles or mean and standard deviation, categorical variables as frequencies and percentages. Efficacy and safety endpoints were compared using the Cox proportional hazards model to produce unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) between patients with and without CLI at randomisation. Adjustment models were derived from a prespecified set of candidate variables using backward selection with a significance level (α) to stay in the model set to 0.05. The randomised treatment effect (ticagrelor vs. clopidogrel) in patients with and without CLI was derived from a Cox proportional hazards model with CLI status and randomised treatment as co-variables. The interaction between randomised treatment and CLI status was tested by expanding the previous model to add such interaction. The proportional hazard assumption was tested using the Schoenfeld residuals method and was satisfied for all endpoints. Kaplan—Meier curves were used to describe the cumulative incidence of the primary efficacy endpoint and all cause death. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographics

Of the 13,885 patients included in EUCLID, 643 (4.6%) had CLI at baseline (Table 1). Most had rest pain (59%) and 41% had major or minor tissue loss. Compared with the 13,239 patients with PAD without CLI, the 643 with CLI were older, more commonly from Central or South America or Asia, and had a lower body weight. Europe and North America included more non-CLI than CLI patients. The female inclusion rate was equal in the two subgroups. The proportion of patients included on the basis of a prior revascularisation or ABI/TBI criteria did not differ between the CLI and non-CLI groups. However, prior revascularisation and an ABI >0.80 was found in 30.5% of the CLI group and in 46.8% of the non-CLI patients. Patients with CLI had significantly lower ABI or TBI values, irrespective of inclusion criteria, although the numerical difference was limited (mean ABI = 0.55 and 0.63, respectively, for those with and without CLI included after prior revascularisation). Both major and minor amputations were more common in patients with CLI at baseline. The proportion of open surgical versus endovascular revascularisation was 44.2% and 55.8%, respectively, in the CLI group, and corresponding proportions were 36.0% and 54.0% among non-CLI patients.

Medical history

Diabetes mellitus was more common in those with CLI (49.3% vs. 38.0%; $p < 0.0001$), while a history of hypertension, hyperlipidemia, and current smoking was less frequent among those with CLI (Table 1). In addition, a history of coronary artery and carotid artery disease as reported was less prevalent in those with CLI. The majority of patients with CLI had only lower limb PAD, while those without CLI were more likely to have two or three vascular beds diseased.

Patients with CLI used less aspirin, statins, and angiotensin receptor blockers as compared with those without CLI. Clopidogrel and cilostazol were used more frequently by those with CLI. Dual antiplatelet therapy (aspirin and clopidogrel) use was similar among patients with and without CLI.

Endpoints

The primary efficacy endpoint, the composite of cardiovascular death, myocardial infarction, or ischaemic stroke, occurred more frequently among patients with CLI compared with those without CLI (Table 2, Fig. 1) with a rate of 8.85 versus 4.28 per 100 patient years (unadjusted HR 2.07 [95% CI 1.72—2.48]; $p < 0.0001$), and this difference remained significant after adjustment for baseline characteristics according to footnotes in Table 2, (HR 1.43 [95% CI 1.16—1.76]; $p = 0.0009$). Myocardial infarction was numerically increased for the CLI group after adjustment (HR 1.37 [95% CI 0.98—1.91]; $p = 0.0668$), while ischaemic stroke was significantly increased (HR 1.87 [95% CI 1.24—2.83]; $p = 0.0027$). All cause mortality was also increased in those with CLI (HR 2.58 [95% CI 2.16—3.10]; $p < 0.0001$), and this difference was still significant after adjustment (HR 1.60 [95% CI 1.31—1.97]; $p < 0.0001$) (Table 2, Fig. 2). Both cardiovascular and non-cardiovascular death were increased in the CLI group (adjusted HR 1.62 [95% CI 1.24—2.11]; $p = 0.0004$ and HR 1.63 [95% CI 1.17—2.27]; $p = 0.0041$, respectively). Cardiovascular death accounted for 61% of all deaths in the CLI group and the corresponding rate in the non-CLI group was 57%. When ALI requiring hospitalisation with MACE was added to the adjustment model, significant differences remained (adjusted HR 1.38 [95% CI 1.13—1.69]; $p = 0.0016$). In contrast, the rates of post-randomisation lower extremity or coronary revascularisation were not independently increased in patients with CLI. Major amputation was increased among those with CLI (adjusted HR 3.41 [95% CI 2.39—4.87]; $p < 0.0001$); a corresponding difference was noted for minor amputations (adjusted HR 2.10 [95% CI 1.42—3.12]; $p = 0.0002$). Bleeding (TIMI major, intracranial, fatal) did not differ between patients with and without CLI. Minor bleeding, however, was slightly more common in those with CLI (adjusted HR 1.90 [95% CI 1.02—3.52]; $p = 0.0424$).

DISCUSSION

The EUCLID trial was designed primarily to enroll patients with intermittent claudication or patients who had had a prior revascularisation, and patients with clinical symptoms of CLI, rest pain, or ulcers and gangrene, were also included. However, generally accepted hemodynamic criteria to verify CLI by ABI or TBI were not required, underlining that EUCLID is not primarily a CLI trial. Patients with CLI in the EUCLID trial were predominantly symptomatic with rest pain, with fewer patients having tissue loss meaning that the CLI was relatively mild. There were proportionally more CLI patients included from Central and South America as well as from Asia, while Europe and North America included more non-CLI individuals. Whether this is a random finding, has an epidemiological background, or just reflects the population that seeks advice cannot be ascertained.

The subset of patients with CLI in EUCLID had a higher proportion of diabetes mellitus compared with those without CLI. In contrast, patients with CLI had a lower prevalence of the other standard risk factors associated with systemic atherosclerosis (less smoking, hypertension, and hyperlipidemia). Unexpectedly, a history of coronary or carotid artery disease was less common in those with CLI, who also predominantly had only lower extremity PAD. Despite these differences, patients with CLI had an unadjusted twofold increased risk of the primary endpoint compared with patients without CLI. After adjustment for baseline factors, the risk was increased by 43% and all cause mortality was increased by 60%. In patients with CLI, 39% of all cause mortality was non-cardiovascular indicating that a substantial number of deaths in CLI are not directly related to atherothrombosis, reflecting the overall burden of non-

Table 1. Baseline characteristics by CLI.

Characteristic	CLI status at randomisation		*p*-value
	Yes ($N = 643$)	No ($N = 13,239$)	
Age, median (25th, 75th), years	68 (61, 75)	66 (60, 72)	0.0001
Female, no. (%)	172 (26.7%)	3716 (28.1%)	0.4670
Region, no. (%)			<0.0001
Central/South America	106 (16.5%)	1634 (12.3%)	
Europe	313 (48.7%)	7182 (54.2%)	
Asia	107 (16.6%)	1495 (11.3%)	
North America	117 (18.2%)	2928 (22.1%)	
Weight, median (25th, 75th), kg	74 (63, 86)	77 (66, 88)	<0.0001
Inclusion criteria for randomisation			0.2652
Previous revascularisation, no. (%)	351 (54.6%)	7522 (56.8%)	
ABI value, mean (SD)	0.67 (0.29)	0.78 (0.22)	<0.0001
ABI or TBI criteria, no. (%)	292 (45.4%)	5717 (43.2%)	
ABI value, mean (SD)	0.55 (0.21)	0.63 (0.15)	<0.0001
TBI value, mean (SD)	0.49 (0.15)	0.52 (0.22)	0.5928
Ankle pressure ≤50 mm Hg, no. (%)	161 (25.8%)	1173 (9.0%)	<0.0001
Ankle pressure ≤70 mm Hg, no. (%)	313 (50.2%)	3563 (27.3%)	<0.0001
Toe pressure ≤30 mm Hg, no./No. (%)	2/12 (16.7%)	8/121 (6.6%)	0.2233
Toe pressure ≤50 mm Hg, no./No. (%)	3/12 (25.0%)	30/121 (24.8%)	1.0000
Limb symptoms, no. (%)			
Asymptomatic	0 (0.0%)	2601 (19.6%)	
Mild or moderate claudication	0 (0.0%)	7410 (56.0%)	
Severe claudication	0 (0.0%)	3228 (24.4%)	
Pain at rest	378 (58.8%)	0 (0.0%)	
Minor tissue loss	207 (32.2%)	0 (0.0%)	
Major tissue loss	58 (9.0%)	0 (0.0%)	
Major amputation above the ankle, no. (%)	66 (10.3%)	272 (2.1%)	<0.0001
Minor amputation, no. (%)	107 (16.6%)	498 (3.8%)	<0.0001
Medical history, no. (%)			
Stroke	62 (9.6%)	1081 (8.2%)	0.1833
Transient ischaemic attack	27 (4.2%)	480 (3.6%)	0.4491
Coronary artery disease	163 (25.3%)	3868 (29.2%)	0.0349
Myocardial infarction	108 (16.8%)	2414 (18.2%)	0.3558
Carotid stenosis or carotid revascularisation	78 (12.1%)	2379 (18.0%)	0.0002
Number of vascular beds affected			0.0091
1	399 (62.1%)	7403 (55.9%)	
2	187 (29.1%)	4500 (34.0%)	
3	57 (8.9%)	1336 (10.1%)	
Diabetes mellitus type I or II	317 (49.3%)	5027 (38.0%)	<0.0001
Hypertension	477 (74.2%)	10,379 (78.4%)	0.0115
Hyperlipidemia	402 (62.5%)	10,077 (76.1%)	<0.0001
Tobacco use, no. (%)			<0.0001
Never smoker	198 (30.9%)	2786 (21.2%)	
Former smoker	287 (44.8%)	6242 (47.4%)	
Current smoker	155 (24.2%)	4134 (31.4%)	
Medications before randomisation, no. (%)			
Aspirin	357 (55.5%)	8913 (67.3%)	<0.0001
Clopidogrel	257 (40.0%)	4216 (31.8%)	<0.0001
DAPT (ASA and clopidogrel)	104 (16.2%)	2163 (16.3%)	0.9126
Statin	412 (64.1%)	9768 (73.8%)	<0.0001
ACE inhibitor	250 (38.9%)	5384 (40.7%)	0.3674
Angiotensin receptor blocker	136 (21.2%)	3352 (25.3%)	0.0173
Cilostazol	123 (19.1%)	1972 (14.9%)	0.0034

ABI = ankle brachial index; ACE = angiotensin converting enzyme; ASA = aspirin; CLI = critical limb ischaemia; DAPT = dual antiplatelet therapy; TBI = toe brachial index.

cardiovascular mortality in this population in which cancer frequently co-exists.[18] However, the rate of all cause mortality of 8.7 events per 100 patient years is low compared with previous reports, which may reflect the predominance of ischaemic rest pain as a less severe manifestation of CLI. Historically, 1 year mortality rates have been reported at up to 20—25% in patients with CLI treated by revascularisation, medical treatment, or amputation.[1] The corresponding 1

Table 2. Efficacy and safety endpoints by CLI status at randomisation.

	CLI status at randomisation		HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
	Yes Rate (events)[a]	No Rate (events)[a]	CLI vs. no CLI		CLI vs. no CLI	
Efficacy endpoints						
CV death, MI, or ischaemic stroke	8.85 (124)	4.28 (1366)	2.07 (1.72–2.48)	<0.0001	1.43 (1.16–1.76)[b]	0.0009
Death from any cause	8.73 (131)	3.40 (1131)	2.58 (2.16–3.10)	<0.0001	1.60 (1.31–1.97)[c]	<0.0001
CV death	5.21 (77)	1.90 (628)	2.75 (2.17–3.48)	<0.0001	1.62 (1.24–2.11)[c]	0.0004
Non-CV death	3.38 (50)	1.43 (472)	2.38 (1.78–3.19)	<0.0001	1.63 (1.17–2.27)[c]	0.0041
MI	3.18 (45)	1.98 (638)	1.60 (1.18–2.17)	0.0023	1.37 (0.98–1.91)[d]	0.0668
Stroke	1.95 (28)	0.96 (311)	2.03 (1.38–2.99)	0.0003	1.76 (1.18–2.61)[e]	0.0053
Ischaemic stroke	1.81 (26)	0.84 (274)	2.14 (1.43–3.20)	0.0002	1.87 (1.24–2.83)[e]	0.0027
CV death, MI, ischaemic stroke, or ALI requiring hospitalisation	9.85 (136)	4.86 (1535)	2.03 (1.70–2.41)	<0.0001	1.38 (1.13–1.69)[f]	0.0016
Hospitalisation for ALI	1.18 (17)	0.66 (215)	1.76 (1.08–2.89)	0.0244	1.35 (0.80–2.29)[g]	0.2601
Lower limb revascularisation	7.01 (93)	5.40 (1644)	1.29 (1.05–1.59)	0.0175	1.19 (0.96–1.49)[h]	0.1178
Coronary or peripheral revascularisation	8.80 (114)	7.95 (2346)	1.10 (0.91–1.33)	0.3128	1.10 (0.90–1.33)[i]	0.3589
Major amputation	3.91 (54)	0.50 (162)	7.74 (5.69–10.53)	<0.0001	3.41 (2.39–4.87)[j]	<0.0001
Minor amputation	2.78 (39)	0.48 (158)	5.63 (3.97–8.00)	<0.0001	2.10 (1.42–3.12)[j]	0.0002
Safety endpoints[k]						
TIMI major bleeding	1.14 (14)	0.74 (208)	1.54 (0.90–2.65)	0.1172	1.46 (0.85–2.51)	0.1730
TIMI minor bleeding	0.89 (11)	0.50 (140)	1.78 (0.96–3.28)	0.0667	1.90 (1.02–3.52)	0.0424
Intracranial bleeding	0.24 (3)	0.23 (65)	1.05 (0.33–3.33)	0.9367	0.93 (0.29–2.95)	0.8957
Fatal bleeding	0.24 (3)	0.10 (27)	2.52 (0.76–8.31)	0.1290	2.04 (0.62–6.78)	0.2425

ALI = acute limb ischaemia; CLI = critical limb ischaemia; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; TIMI = thrombolysis in myocardial infarction.

[a] Rate per 100 patient years of follow-up (no. of events).

[b] Adjusted for diabetes, sex, inclusion criteria for randomisation, region, age, weight, ABI value, eGFR, tobacco use, history of stroke and MI, number of vascular beds affected, statins before randomisation, and history major and minor amputations.

[c] Adjusted for diabetes, sex, region, age, weight, ABI value, eGFR, history of stroke and MI, clopidogrel, statins and angiotensin receptor blockers before randomisation, and history of major and minor amputations.

[d] Adjusted for age, sex, inclusion criteria for randomisation, region, ABI value, eGFR, tobacco use, aspirin, diabetes, history of myocardial infarction, prior PCI, number of vascular beds affected.

[e] Adjusted for region, history of stroke, diabetes, tobacco use, history of minor amputations and age.

[f] Adjusted for diabetes, sex, inclusion criteria for randomisation, region, age, weight, ABI value, eGFR, tobacco use, history of stroke and MI, number of vascular beds affected, clopidogrel and statins before randomisation, and history major and minor amputations.

[g] Adjusted for inclusion criteria for randomisation, region, ABI value and statin and angiotensin receptor blockers before randomisation.

[h] Adjusted for diabetes, inclusion criteria for randomisation, region, ABI value, eGFR, tobacco use, and aspirin and clopidogrel before randomisation.

[i] Adjusted for diabetes, inclusion criteria for randomisation, region, ABI value, tobacco use, history of PCI, number of vascular beds affected, and aspirin, clopidogrel, and angiotensin receptor blockers before randomisation.

[j] Adjusted by diabetes, inclusion criteria for randomisation, ABI value, history major and minor amputations, weight and statin before randomisation.

[k] Adjusted for sex, region, age and clopidogrel before randomisation.

year (after randomisation) mortality rate in the present study was only 8.9%. The patients with CLI in EUCLID, however, may have been treated for CLI at any time earlier than 3 months before randomisation or not treated at all. There was a trend for more limb adverse events in terms of hospitalisation for ALI or lower limb revascularisation in the CLI group. There is some evidence that amputation free survival has improved in recent years for severely diseased patients with CLI who are not candidates for revascularisation.[19] The Tamaris trial showed a 1 year mortality rate of 16% and a major amputation rate of 23%.[4] These data relate to patients enrolled in trials of medical therapy (drugs or biologics), in which patients are managed in an optimal way, a fact that may contribute to a better outcome. In everyday practice, higher mortality rates are commonly reported. As an example, a recent Japanese study of 662 revascularised and non-revascularised patients with CLI confirmed a 1 year all cause mortality rate of 33.7%.[20] Data from the Swedvasc Registry[21] have shown that 36 months after revascularisation of patients with CLI, the rate of cardiovascular death, myocardial infarction, and ischaemic stroke was as high as 34% over the 3 years. In that study, besides the fact that 55% of patients with CLI were not offered best medical treatment, it was shown that aspirin, the most commonly used antiplatelet agent, was not associated with a reduction of cardiovascular events.

In reviewing results of the current analysis, there may be discussion about whether or not the CLI group in EUCLID is

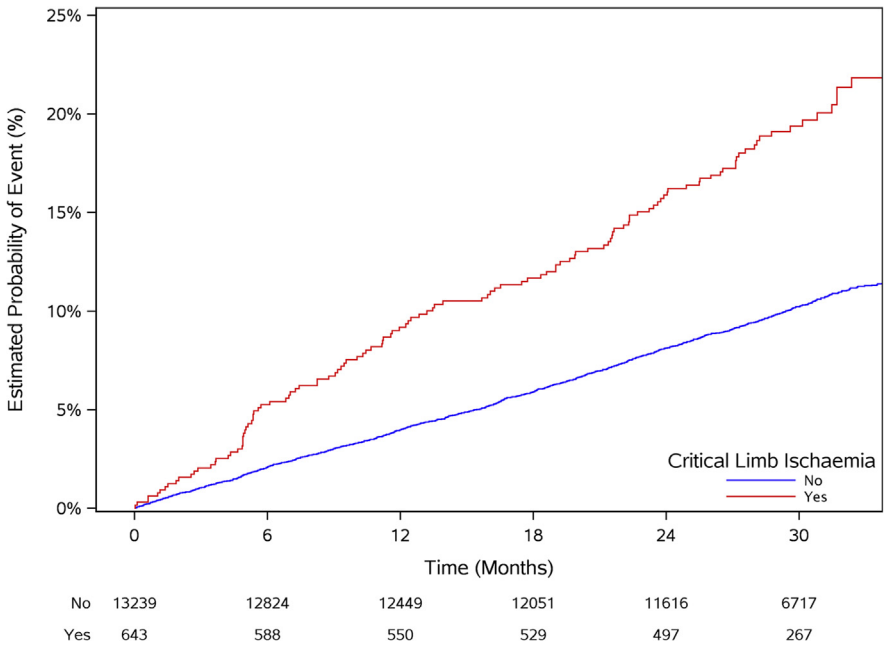

Figure 1. Cardiovascular death, myocardial infarction, or ischaemic stroke by critical limb ischaemia status at randomisation.

representative of CLI in general or if these patients had less advanced disease, as both mortality and amputation rates were low. The CLI group comprised 4.6% of all patients in the EUCLID study. In PAD overall, a proportion of 1—3% of patients with CLI is commonly reported.[1] As up to 50% of all patients with PAD identified by a low ABI are asymptomatic, it is reasonable to predict an up to 6% rate of CLI in a symptomatic PAD population, corresponding to the findings in the present trial. On the other hand, nearly 60% of the CLI group had only rest pain and no wounds or gangrene. Patients requiring revascularisation within the next 3 months after randomisation were excluded from participation in the study, which further reduces the severity of the ischaemic state in the included CLI cohort.

Furthermore, the mean ABI value for the non-revascularised CLI group at randomisation was relatively high (mean 0.55). Hemodynamic criteria to verify CLI are usually an ankle pressure of $\leq$50 mm Hg for patients with rest pain and $\leq$70 mm Hg for those with ischaemic foot lesions. In the present CLI cohort, 25.8% had an ankle pressure of $\leq$50 mmHg and 50.2% had an ankle pressure $\leq$70 mmHg. Toe pressures were measured in a minority of patients. Based on these findings it seems reasonable to conclude that included patients had more stable and less

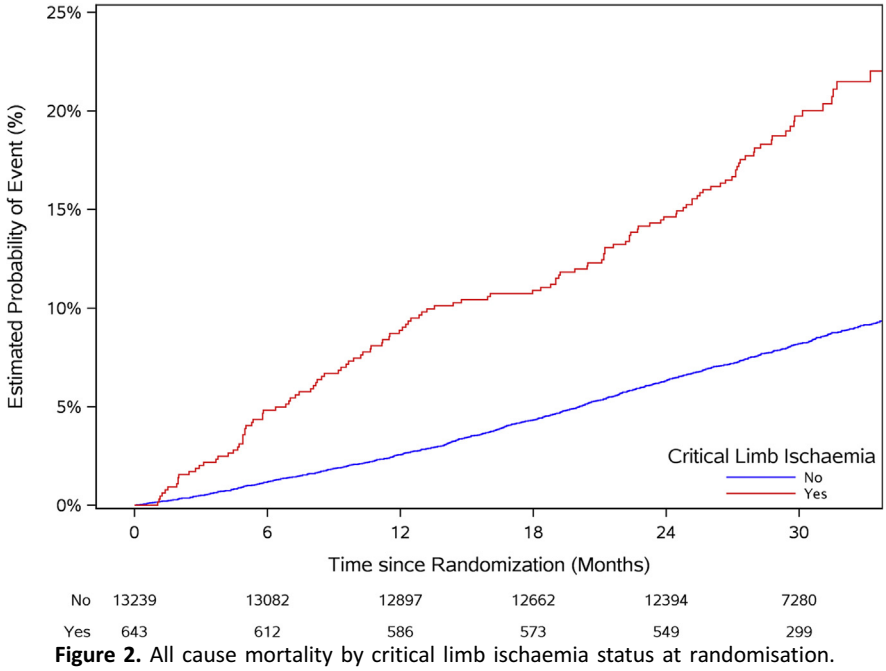

Figure 2. All cause mortality by critical limb ischaemia status at randomisation.

advanced CLI. This selection bias may partly be related to an intention of investigators to enroll patients with a better prospect for survival. Furthermore, it cannot be ruled out that some patients and investigators incorrectly interpreted leg symptoms as ischaemic rest pain.

Despite these findings and the lesser burden of traditional cardiovascular risk factors and less polyvascular disease, the CLI group in EUCLID had a higher risk of MACE and greater cardiovascular and all cause mortality. The increased rate of diabetes mellitus in this group may be a contributing factor. Furthermore, the raised inflammatory response including augmented cytokine, adhesion molecule, and complement activity levels that are well known in PAD are even more pronounced in CLI,[22,23] as well as after revascularisation.[24] The EUCLID trial, however, did not investigate any measures of the inflammatory response, and conclusions can therefore not be drawn in this regard. It is also reasonable to assume that severe symptoms such as rest pain and painful foot lesions induce worsening of the general condition.

This secondary analysis corresponds to the main EUCLID study results with regard to the primary efficacy endpoint for ticagrelor and clopidogrel monotherapy in patients with PAD.[17] Previous studies of ticagrelor included patients with acute coronary syndrome[14] or prior myocardial infarction[15,25] and patients with PAD constituted a subgroup. Patients in these studies were also on aspirin, while those in EUCLID received monotherapy with ticagrelor or clopidogrel. Theoretically, dual antiplatelet therapy might be of value in CLI as platelet and monocyte activation is higher in this group, as shown in patients scheduled for revascularisation.[11] In a randomised controlled trial in patients undergoing surgery for CLI, it was shown that dual antiplatelet therapy (clopidogrel plus aspirin) further reduced biomarkers for atherothrombosis compared with aspirin alone.[26] From a clinical point of view, however, results from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management, and Avoidance) trial[27] and a post-hoc analysis of the PAD subgroup[28] do not support use of dual antiplatelet therapy in stable PAD. Evidence to support recommendations for antithrombotic treatment specifically in CLI is still missing, which means a gap in the recommendations of recent guidelines.[8,29] It is reasonable to assume that aspirin treatment alone is not optimal, but to date relevant studies have not been performed to enable conclusions. It is evident from EUCLID that clopidogrel and ticagrelor are equally effective and well tolerated in patients with symptomatic PAD; however, they are not optimal in the prevention of MACE and MALE, specifically in patients with CLI. There were some statistically significant treatment by CLI subgroup interactions

Table 3. Randomised treatment effect in patients with and without CLI at randomisation.

	CLI at randomisation			No CLI at randomisation			Interaction
	Ticagrelor Rate (events)[a]	Clopidogrel Rate (events)[a]	HR (95% CI) ticagrelor vs. clopidogrel	Ticagrelor Rate (events)[a]	Clopidogrel Rate (events)[a]	HR (95% CI) ticagrelor vs. clopidogrel	*p*-value
Efficacy endpoints							
CV death, MI, or ischaemic stroke	8.51 (60)	9.19 (64)	0.93 (0.65—1.32)	4.36 (691)	4.21 (675)	1.03 (0.93—1.15)	0.5599
Death from any cause	9.49 (71)	7.98 (60)	1.19 (0.84—1.68)	3.35 (557)	3.44 (574)	0.98 (0.87—1.10)	0.2767
CV death	5.97 (44)	4.45 (33)	1.35 (0.86—2.12)	1.94 (319)	1.87 (309)	1.04 (0.89—1.22)	0.2866
Non-CV death	3.39 (25)	3.37 (25)	1.01 (0.58—1.75)	1.37 (225)	1.49 (247)	0.92 (0.77—1.10)	0.7461
MI	2.40 (17)	3.95 (28)	0.61 (0.33—1.12)	2.08 (332)	1.89 (306)	1.10 (0.94—1.28)	0.0630
Stroke	1.12 (8)	2.77 (20)	0.40 (0.18—0.92)	0.88 (142)	1.04 (169)	0.85 (0.68—1.06)	0.0905
Ischaemic stroke	1.12 (8)	2.49 (18)	0.45 (0.20—1.03)	0.76 (123)	0.93 (151)	0.82 (0.65—1.04)	0.1760
CV death, MI, ischaemic stroke, or ALI requiring hospitalisation	9.84 (68)	9.87 (68)	1.00 (0.71—1.39)	4.90 (771)	4.81 (764)	1.02 (0.92—1.13)	0.9029
ALI requiring hospitalisation	1.56 (11)	0.82 (6)	1.90 (0.70—5.13)	0.65 (106)	0.67 (109)	0.98 (0.75—1.28)	0.2162
Lower limb revascularisation	5.69 (38)	8.34 (55)	0.69 (0.45—1.04)	5.31 (808)	5.49 (836)	0.97 (0.88—1.07)	0.1077
Coronary or peripheral revascularisation	6.85 (45)	10.80 (69)	0.64 (0.44—0.93)	7.91 (1166)	7.99 (1180)	0.99 (0.91—1.07)	0.0228
Major amputation	5.12 (34)	2.79 (20)	1.79 (1.03—3.11)	0.41 (66)	0.59 (96)	0.69 (0.51—0.95)	0.0029
Minor amputation	2.60 (18)	2.96 (21)	0.87 (0.46—1.63)	0.46 (75)	0.51 (83)	0.91 (0.67—1.24)	0.9108
Safety endpoints							
TIMI major bleeding	1.16 (7)	1.12 (7)	1.03 (0.36—2.93)	0.77 (106)	0.70 (102)	1.10 (0.84—1.45)	0.9051
TIMI minor bleeding	1.48 (9)	0.32 (2)	4.61 (1.00—21.36)	0.55 (75)	0.45 (65)	1.22 (0.87—1.70)	0.0961
Intracranial bleeding	0.33 (2)	0.16 (1)	2.02 (0.18—22.32)	0.23 (32)	0.23 (33)	1.03 (0.63—1.67)	0.5814
Fatal bleeding	0.00 (0)	0.48 (3)	—	0.07 (10)	0.12 (17)	0.62 (0.29—1.36)	—

ALI = acute limb ischaemia; CLI = critical limb ischaemia; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; TIMI = thrombolysis in myocardial infarction.

[a] Rate per 100 patient years of follow-up (no. of events).

observed in Table 3 (in the CLI subgroup fewer coronary or peripheral revascularisations but more major amputations on ticagrelor compared with clopidogrel). However these interactions are probably of no clinical significance as there was no treatment effect in the overall trial, there was no adjustment for multiple comparisons and the CLI population was a small subgroup of the overall trial.

In conclusion, the present study of patients with CLI in the EUCLID trial has shown a considerably increased risk of cardiovascular and limb adverse events, compared with those without CLI, mainly including patients with intermittent claudication. This is despite selection of patients with less advanced stages of CLI. The results highlight a far from optimal antithrombotic treatment, and further studies in a carefully defined CLI population are required.

ACKNOWLEDGMENTS

Elizabeth Cook of the Duke Clinical Research Institute provided editorial assistance.

CONFLICTS OF INTEREST

Norgren: Steering committee fees from AstraZeneca, Bayer, AnGes MG, and Pluristem Therapeutics, advisory board fees from Cesca Therapeutics, consulting fees from Mitsubishi Tanabe Pharma, and research grants from AnGes MG and Mitsubishi Tanabe Pharma.
Patel: Consulting fees from AstraZeneca, Bayer, CSI, Genzyme, Janssen Research & Development, Medtronic, and Merck, research grants from AstraZeneca, CSI, HeartFlow, Janssen Research & Development, Maquet, Medtronic, and the NHLBI.
Hiatt: Research funding to CPC clinical research from AstraZeneca, Bayer, Jansen, Pluristem.
Wojdyla, Jones, Rockhold: None to report.
Fowkes: Consulting fees from Bayer and Merck.
Baumgartner: Steering committee fees from AstraZeneca, advisory board fees from Bayer and Sanofi, research grants from Abbott Vascular, Cook Medical, Optimed, Terumo Medical, Promedics, Amgen, and Boston Scientific.
Mahaffey: Consulting fees from BAROnova, Bayer, Bio2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb, Cubist, Eli Lilly, Epson, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, MyoKardia, Omthera Pharmaceuticals, Portola Pharmaceuticals, Purdue Pharma, the Medicines Company, Theravance, Vindico, and WebMD, and research grants from Amgen, Daiichi-Sankyo, Johnson & Johnson, Medtronic, Merck, St. Jude Medical, and Tenax Therapeutics, and equity in BioPrint Fitness.
Berger: Advisory board fees from Janssen, Merck, and Takeda.
Katona, Held, Blomster: Employees of AstraZeneca.
Bjorck: Consulting fees from AstraZeneca.

FUNDING

This work and the EUCLID study were supported by AstraZeneca.

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