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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.

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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

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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).

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