



Design and rationale for the Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease (EUCLID) trial

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Background Despite overwhelming data demonstrating the efficacy of antiplatelet therapy in heart disease and stroke, data in peripheral artery disease (PAD) are less compelling. Aspirin has modest evidence supporting a reduction in cardiovascular events in patients with PAD, whereas clopidogrel monotherapy may be more effective in PAD. Ticagrelor, a potent, reversibly binding P2Y₁₂ receptor antagonist, is beneficial in patients with acute coronary syndrome and prior myocardial infarction. The EUCLID trial is designed to address the need for effective antiplatelet therapy in PAD to decrease the risk of cardiovascular events.

Study design EUCLID is a randomized, double-blind, parallel-group, multinational clinical trial designed to evaluate the efficacy and safety of ticagrelor compared with clopidogrel for the prevention of major adverse cardiovascular events in subjects with symptomatic PAD. Subjects with established PAD will be randomized in a 1:1 fashion to ticagrelor 90 mg twice daily or clopidogrel 75 mg daily. The primary end point is a composite of cardiovascular death, myocardial infarction, or ischemic stroke. Other end points address limb events including acute leg ischemia, need for revascularization, disease progression by ankle-brachial index, and quality of life. The primary safety objective is Thrombolysis in Myocardial Infarction–defined major bleeding. Recruitment began in December 2012 and was completed in March 2014; 13,887 patients were randomized. The trial will continue until at least 1,364 adjudicated primary end points occur.

Conclusions The EUCLID study is investigating whether treatment with ticagrelor versus clopidogrel, given as antiplatelet monotherapy, will reduce the incidence of cardiovascular and limb-specific events in patients with symptomatic PAD. (*Am Heart J* 2016;175:86-93.)

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Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis and part of the cardiovascular (CV) disease continuum. Global prevalence increased by nearly 25% from 2000 to 2010 and is estimated to affect >200 million subjects worldwide [1]. Patients with PAD have elevated levels of platelet activity and are at substantial increased risk for platelet-mediated adverse CV events, such as myocardial infarction (MI), ischemic stroke, and CV death [2]. Clinical manifestations associated with lower extremity PAD include decrements in functional capacity and quality of life, including loss of limb in severely affected patients.

Current treatment guidelines recommend antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in patients with PAD [3–5] and specifically recommend monotherapy with a daily dose of aspirin 75–325 mg or clopidogrel 75 mg as safe and effective antiplatelet therapy. However, a meta-analysis of aspirin versus placebo or control in 18 prospective randomized trials

comprising 5,269 subjects with PAD demonstrated no statistically significant reduction in CV events with aspirin therapy [6]. More recent studies of aspirin in subjects with asymptomatic PAD or PAD with diabetes also failed to show a benefit of aspirin [5,7-9].

Clopidogrel in PAD

Clopidogrel, an irreversible P2Y₁₂ receptor antagonist, 75 mg daily is recommended as an alternative antiplatelet therapy to aspirin in individuals with PAD. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events study demonstrated significant but modest benefit of clopidogrel monotherapy over aspirin monotherapy in patients with recent MI, stroke, or symptomatic PAD over the 36-month study duration [10]. The beneficial effect was mainly driven by the 24% relative risk reduction seen in the composite end point in the PAD subgroup (*P* for interaction < .05). Dual antiplatelet therapy has not been shown to significantly decrease CV events in the setting of stable PAD [11]. Accordingly, the European Society of Cardiology, Inter-Society Consensus for the Management of Peripheral Arterial Disease, American College of Cardiology Foundation/American Heart Association, and American College of Chest Physicians guidelines do not recommend routine dual antiplatelet therapy in PAD on the basis of there being no additional benefit and an increased bleeding risk [3-5,12].

Ticagrelor

Ticagrelor is a reversibly binding, potent, oral adenosine diphosphate P2Y₁₂ receptor blocker. The Study of Platelet Inhibition and Patient Outcomes (PLATO) [13] trial demonstrated superiority of ticagrelor over clopidogrel in the prevention of fatal and nonfatal CV events in patients with acute coronary syndrome on background aspirin therapy. The primary safety end point, PLATO-defined "major bleeding," did not differ significantly from clopidogrel. In the subgroup of patients with PAD in the PLATO trial, the reduction in ischemic events with ticagrelor versus clopidogrel was consistent with the overall trial results [14].

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction (PEGASUS-TIMI 54) 54 trial randomized 21,162 patients with prior MI 1 to 3 years earlier to ticagrelor 90 mg, 60 mg, or placebo twice daily on a background of low-dose aspirin for a median of 33 months. Both ticagrelor doses reduced the primary composite end point of CV death, MI, or stroke as compared with placebo. Rates of TIMI major bleeding were higher with both ticagrelor doses, with no difference in the rates of intracranial hemorrhage or fatal bleeding among the 3 groups [15].

The Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease (EUCLID) study is being

conducted to determine whether treatment with ticagrelor, given as antiplatelet monotherapy, compared with clopidogrel monotherapy will reduce the incidence of atherothrombotic ischemic events as measured by the composite end point of CV death, MI, or ischemic stroke in a population with established PAD.

Study design and population

EUCLID is an international, multicenter, randomized, double-blind, parallel-group, end point-driven phase IIIb study to assess the prevention of atherothrombotic events with ticagrelor 90 mg twice daily compared with clopidogrel 75 mg daily in patients with established PAD. The study design is shown in Figure (ClinicalTrials.gov no., NCT01732822) [16].

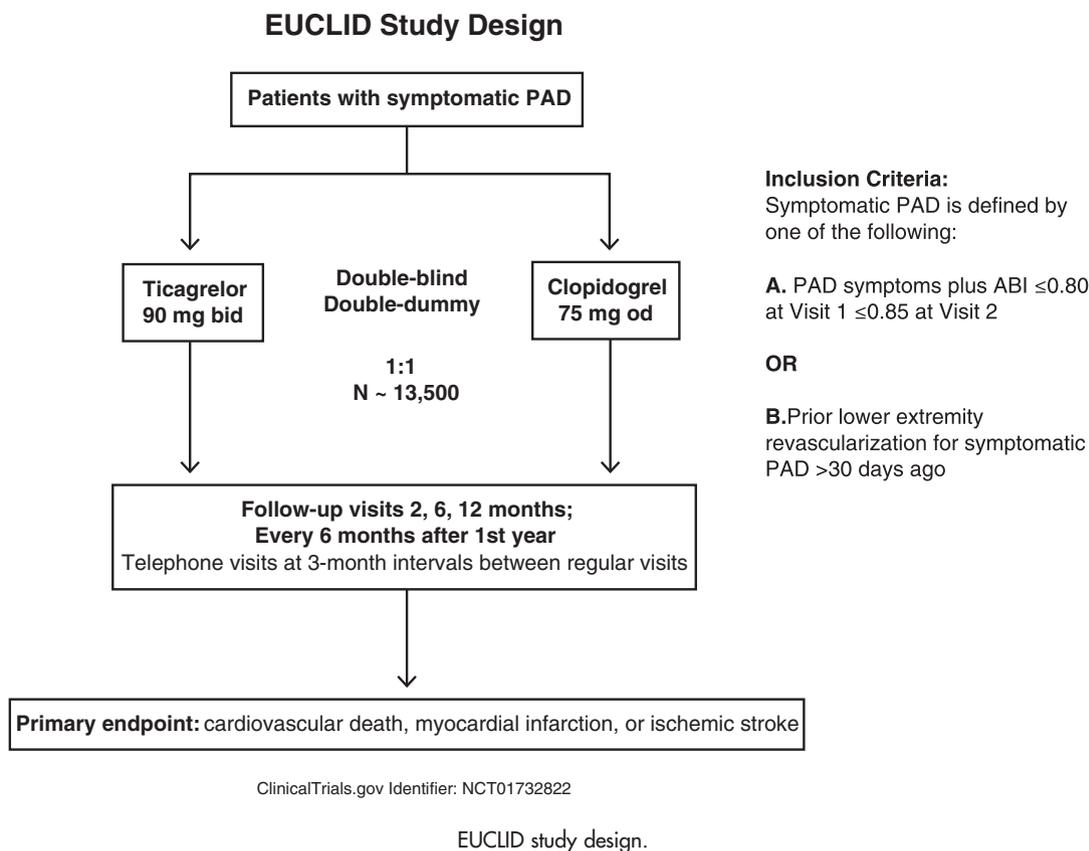
The inclusion criteria for EUCLID are designed to enroll a representative sample of subjects with PAD. Study patients must be ≥50 years of age with symptomatic PAD, defined by 1 of the following: (1) ankle-brachial index (ABI) ≤0.80 and lower extremity symptoms, or (2) prior lower extremity revascularization (Table I).

For patients qualifying via the ABI criteria, 2 distinct measurements are required—at entry, the ABI measurement must be ≤0.80; and at the subsequent randomization visit, ≤0.85. This is done to improve the specificity of the ABI to ensure that patients enrolled have substantial hemodynamic evidence of PAD (given the 0.10 test-retest variation, an ABI of 0.80 ensures that the upper bound would be ≤0.90) [17,18]. If ABI is ≥1.40, a toe-brachial index (TBI) ≤0.60 at visit 1 and ≤0.65 at visit 2 is alternatively accepted. Patients with prior lower extremity revascularization for symptomatic PAD qualify for enrollment if revascularization was >30 days before randomization, irrespective of present leg symptoms and hemodynamics at the time of study screening.

Key exclusion criteria include planned use of dual antiplatelet therapy, requirement of aspirin, history of bleeding diathesis, treatment with anticoagulation, or *poor metabolizer status for CYP2C19*, defined as possessing a genotype consisting of 2 loss-of-function alleles. All patients must provide written informed consent for participation. A complete listing of the inclusion/exclusion criteria is provided in Table I.

EUCLID patients were being randomized in a 1:1 ratio to receive either ticagrelor monotherapy or clopidogrel monotherapy. Recruitment began in December 2012 and was completed in March 2014, and 13,887 patients were randomized. Two patients were determined to be double enrolled and randomized (ie, same patient enrolled and randomized at 2 separate sites); therefore, the total number of randomized subjects was 13,885. The baseline characteristics of patients enrolled in EUCLID are shown in Table II. Randomized patients are being followed for all clinical end points and serious adverse events (AEs) until the end of the study, with the primary and several

Figure

**Inclusion Criteria:**

Symptomatic PAD is defined by one of the following:

A. PAD symptoms plus ABI ≤ 0.80 at Visit 1 ≤ 0.85 at Visit 2

OR

B. Prior lower extremity revascularization for symptomatic PAD >30 days ago

secondary end point events confirmed by central adjudication. The trial will continue until at least 1,364 adjudicated primary end points (CV death, MI, or ischemic stroke) have accrued.

The study is being performed in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the corresponding health authorities and ethics boards/institutional review boards for all participating study sites. Enrolled patients gave written informed consent for participation in the trial.

Treatment protocol and follow-up procedures

Treatment selection and compliance

Study drug is administered as either double-blind ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily (ticagrelor or matching placebo versus clopidogrel or matching placebo in the morning and ticagrelor or matching placebo in the evening). The ticagrelor 90-mg dose was well tolerated and showed high and consistent

levels of platelet inhibition in phase II studies, with an acceptable safety profile [19,20]. Moreover, PLATO showed a positive clinical benefit-risk balance with this dose [13]. The clopidogrel 75-mg daily dose was selected because it is the approved maintenance dose in clinical practice. No loading dose is administered because a rapid onset is not required in the stable setting. During the study, it is anticipated that some patients may develop an indication for a loading dose of P2Y₁₂ receptor antagonist. A modified study treatment option is provided to investigators to allow an additional 90 mg of ticagrelor or placebo and up to 600 mg of clopidogrel or placebo as a supplemental loading dose.

Concomitant therapies

All patients in EUCLID are recommended to be on standard CV prevention therapies, including statins, consistent with recommendations for subjects with established PAD. Additional antithrombotic therapy was prohibited including other P2Y₁₂ receptor antagonists, long-term anticoagulants at therapeutic doses, and other platelet inhibitors. Dual antiplatelet therapy at the start of the study was prohibited but allowed if a clinical indication (eg, MI) occurred during the course of follow-up with the allowance

Table 1. Inclusion and exclusion criteria

Inclusion
At least 50 y of age
Symptomatic PAD defined by:
A. PAD symptoms plus ABI criteria
-PAD symptoms consist of classic claudication, other exertional leg discomfort associated with physical limitations from PAD, ischemic rest pain, ischemic ulcers, or gangrene
-ABI ≤ 0.80 at V1 and ≤ 0.85 at V2
-If ABI is ≥ 1.40 , then the TBI must be ≤ 0.60 at V1 and ≤ 0.65 at V2
OR
B. Prior lower extremity revascularization for symptomatic PAD >30 days ago
Written informed consent before any study specific procedures
Exclusion
Poor metabolizer status for CYP2C19, defined as possessing genotype consisting of 2 loss-of-function alleles
Hypersensitivity to clopidogrel or ticagrelor
Patients requiring dual antiplatelet therapy at study entry
Need for long-term oral anticoagulant therapy or long-term low-molecular-weight heparin or long-term treatment with fondaparinux
Planned (and judged necessary) use of ticlopidine, prasugrel, aspirin, or dipyridamole
Planned (and judged necessary) use of omeprazole or esomeprazole.
The use of other proton pump inhibitors is permitted.
Any condition which in the opinion of the investigator would make it unsafe or unsuitable for the patient to participate in this study (eg, active malignancy other than squamous cell or basal cell skin cancer, use of strong or moderate CYP2C19 inhibitors, long-term concomitant treatment with nonsteroidal anti-inflammatory drugs)
Life expectancy <6 m based on investigator's judgment
Planned revascularization (surgical or endovascular) in any vascular territory within the next 3 m
Planned major amputation due to PAD within the next 3 m or major amputation due to PAD within the last 30 d
Patients who have suffered a stroke during the past 3 m
Dementia likely to jeopardize understanding of information pertinent to study conduct or compliance to study procedures
Severe hypertension that may put the patient at risk
Patients considered to be at risk of bradycardic events (eg, known sick sinus syndrome or second- or third-degree atrioventricular block) unless already treated with a permanent pacemaker
Known severe liver disease (eg, ascites and/or clinical signs of coagulopathy)
Renal failure requiring dialysis
A clinically important bleeding diathesis, hemostatic or coagulation disorder, or systemic bleeding
History of previous intracranial bleed at any time, gastrointestinal bleed within the past 6 m, or major surgery within 30 d (if the surgical wound is judged to be associated with an increased risk of bleeding)
Clinically important thrombocytopenia or neutropenia
Women of child-bearing potential (ie, those who are not chemically or surgically sterilized or who are not postmenopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR women who have a positive pregnancy test result at visit 1
Concern for inability of the patient to comply with study procedures and/or follow-up (eg, alcohol or drug abuse)
Previous randomization in the present study
Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at the study center)

for the addition of open-label aspirin. Planned concomitant treatment with any approved phosphodiesterase D₃ inhibitor for claudication (cilostazol, pentoxifylline, or naftidro-

furyl) is permitted. Additional details are described in online Appendix A.

Recommendations for patients undergoing procedures

For elective cardiac and major noncardiac surgery which in the opinion of the investigator poses a risk for clinically major bleeding, patients are advised to stop study treatment 5 days before the procedure and resume when determined appropriate by the treating physician. For other surgery or invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator. It is also recommended that study medication not be discontinued for significantly longer than 5 days to minimize the risk of thrombotic complications while off study medication.

Visit schedule and follow-up

Randomized patients return for study visits at months 2, 6, and 12 during the first year followed by in-person 6-month visits thereafter until the end of the trial, to be determined when the projected number of at least 1,364 primary efficacy end points is about to be reached. There is a telephone visit every 6 months beginning at month 9 until the end of the trial. During follow-up visits, patients are assessed for adverse and potential end point events. All patients are to undergo an End of Treatment visit when permanently stopping therapy and a follow-up contact approximately 2 weeks after their last dose of study drug. It is recommended that all randomized patients attend the final study visit in person regardless of whether or not they are taking randomized study treatment. Vital status will be assessed in all patients at the end of the trial.

ABI and TBI measurements

The ABI/TBI was measured at visit 1 in all subjects and at both visits 1 and 2 in those enrolled under the ABI/TBI criteria; subsequent ABI/TBI measurements were obtained at the 6-month visit and at the end of the study visit. The measurement ankle vessel and limb used at the first 2 visits were identified and used for all subsequent visits. The first 2 ABI measurements for the first 3 subjects at each site were assessed for quality by the ABI core laboratory (see below).

The ABI/TBI was used to determine eligibility for the study for patients enrolling under ABI criteria. The ABI/TBI will also serve as an exploratory end point in the trial to address the progression of disease over time and to test the hypothesis that ticagrelor reduces the rate of decline in ABI/TBI relative to clopidogrel.

The ABI core laboratory was formed to provide a quality control check on the measurement to ensure that patients meet the ABI inclusion criterion and to avoid misclassification, which could adversely affect the proposed event rate. The ABI core laboratory performed regular data monitoring on ABI/TBI reproducibility at entry and any outliers by site, country, and region. Based

Table II. Baseline characteristics of patients included in EUCLID at study entry (not final data [data as of November 30, 2015])*

	All patients (N = 13885) [†]
Age, median (25th, 75th), y	66.0 (60.0, 73.0)
Male sex	9997 (72.0)
Inclusion criteria for randomization	
Prior revascularization	7878 (56.7)
ABI/TBI criterion	6007 (43.3)
ABI findings at randomization, median (25th, 75th) [‡]	0.70 (0.58, 0.82)
Medical history	
History of stroke	1134 (8.2)
History of TIA	506 (3.6)
MI	2518 (18.1)
Prior PCI or CABG	3218 (23.2)
Diabetes mellitus	5342 (38.5)
Hypertension requiring drug therapy	10839 (78.1)
Hyperlipidemia requiring drug therapy	10462 (75.4)
Tobacco use	
Never smoked	2990 (21.7)
Current smoker	4285 (31.0)
Former smoker	6527 (47.3)

Data presented as number (percentage), unless otherwise indicated. TIA, Transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting surgery.

* A patient may meet more than 1 exclusion criteria.

[†]N represents total number of patients, not randomizations. Two patients were determined to be double enrolled (ie, same patient enrolled at 2 separate sites); therefore, the total number of randomized subjects was 13,885.

[‡]ABI (or TBI) 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 highest of the right and left ABIs (or TBIs) is selected.

on cumulative data from the sites and countries, interventions to address excess variability were incremental, starting with site feedback by e-mail and newsletters and extending to site visits to observe the conduct of the ABI/TBI with site personnel and provide retraining as needed.

Study end points

The primary end point in the trial is the composite of CV death, MI, or ischemic stroke. The major secondary end point is the composite of CV death, MI, ischemic stroke, and acute limb ischemia (ALI) requiring hospitalization. ALI was chosen as an end point because of significant limb morbidity observed in subjects with PAD. In addition, antiplatelet therapy with a protease-activated receptor-1 antagonist demonstrated a reduction in major adverse limb events [21]. Definitions of study end points are detailed in online Appendix B.

The primary safety objective of this study is major bleeding using the TIMI definition. Bleeding events will also be adjudicated using the PLATO, Bleeding Academic Research Consortium, and International Society on Thrombosis and Haemostasis definitions. Safety will be assessed through standard ascertainment of site-reported

AEs. Non-serious AEs of interest (ie, bleeding events, dyspnea, renal impairment/increased creatinine, bradyarrhythmia, increased liver function tests, gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding, all malignancies excluding nonmelanoma skin cancers), AE events that are ongoing at the time of permanent discontinuation of study medication due to an AE, and all serious AEs will be reviewed within the context of the earlier safety experience with the drug.

All efficacy and bleeding safety end points are site-reported in an electronic Web-based capture system with submission of supporting source documentation where applicable. Adjudication for each event is performed according to definitions in the EUCLID Clinical End Points Committee Charter (online Appendix B) by an independent, blinded, and trained clinical end points committee with board certification in either cardiology or neurology, depending on the event type.

Statistical considerations

The primary efficacy variable is time from randomization to first occurrence of any event from the primary composite of CV death, MI, or ischemic stroke. The primary variable will be tested at 4.94% significance level (2-sided) to account for 1 planned interim analysis with the overall type I error maintained at 5%. The analysis of all efficacy variables will be based on the intention-to-treat principle using the Cox proportional hazards model with a factor for treatment group. The hazard ratio for ticagrelor versus clopidogrel with 95% CIs will be presented. To address the issue of multiple testing, the confirmatory analysis will comprise a hierarchical test sequence with the primary efficacy variable followed by the secondary efficacy variables in the order listed in Table III. The confirmatory testing will continue at the 4.94% significance level until the first statistically nonsignificant difference of treatment effect in the sequence is observed. Efficacy analyses will be conducted on an intention-to-treat basis among all subjects randomized. The safety evaluation will include all subjects who receive at least 1 dose of study treatment and within 7 days of last study drug dose. Subgroup analyses will be performed to evaluate variation of treatment effect, as well as a test of interaction with treatment for each subgroup variable. The *P* values of the subgroup analyses and interaction tests will not be adjusted for multiple comparisons because the tests are exploratory and will be interpreted descriptively. Subgroup analyses will be performed on the primary efficacy and safety variables. Subgroup analyses will be based on the set of baseline variables (online Appendix Supplementary Table D).

Trial sample size estimation required estimates of event rates in subjects with symptomatic PAD. Estimates were made using the best available data. PAD subgroups were analyzed from prior trials [10,22,23] and registries

Table III. Secondary end points

1. Composite of CV death, MI, ischemic stroke, or hospitalization for ALI
2. CV death
3. MI
4. All-cause mortality
5. The composite of CV death, MI, or all-cause stroke (ischemic or hemorrhagic)
6. Hospitalization for ALI
7. Lower extremity revascularization
8. Composite of all revascularizations (coronary and peripheral [limb, mesenteric, renal, carotid, and other])

[24–28]. Key variables used for event estimation included the proportion of subjects estimated to be enrolled with different ABI cutoffs, prevalence of polyvascular disease, and critical limb ischemia. Data from the PAD subgroup in PLATO demonstrated a similar 15% relative risk reduction as the overall trial results with a greater absolute risk reduction [14].

To detect a true hazard ratio of 0.85, randomization of approximately 11,500 patients was expected to yield 1,596 primary end point events, providing 90% power at 4.94% significance level. The initial sample size was calculated based on the assumption of a 6%–6.5% per year aggregate rate of CV death, MI, or ischemic stroke. Because of the lower-than-expected event rate, the EUCLID Executive Committee modified the trial to preserve adequate power to test the primary study hypothesis. The protocol was amended in December 2013 to increase the sample size from 11,500 to at least 13,500 randomized patients. In March 2015, the targeted number of primary events was reduced from 1,596 to a minimum of 1,364, resulting in a decrease in power from 90% to 85% at 4.94% significance level.

An independent data monitoring committee (DMC) has responsibility for monitoring safety during the trial and will perform at least 1 interim analysis of efficacy when approximately half of the projected primary end points have been accrued and adjudicated. At its discretion, the independent DMC may perform additional efficacy looks. An alpha spending function will govern interim and final statistical testing to control the overall type I error of 5%.

Platelet substudy

A platelet substudy, conducted in the United States, will assess pharmacodynamics as measured through platelet function testing. The platelet substudy is being performed in 10 centers comparing the effects of the study treatments on adenosine diphosphate–induced platelet light transmission aggregation, vasodilator-stimulated phosphoprotein enzyme-linked immunosorbent assay–based assay (BioCytex, Marseille, France), and *VerifyNow* P2Y₁₂ assay (Accumetrics, San Diego, CA).

Study organization

The EUCLID trial is being conducted in 28 countries and 821 sites. The trial operations group is a partnership composed of members of the Duke Clinical Research Institute (DCRI; Durham, NC), Colorado Prevention Center (Denver, CO), and AstraZeneca (London, UK), the trial sponsor (online Appendix C). An executive committee monitors ongoing conduct of the trial. An international steering committee composed of academic experts and national lead investigators for each country is responsible for the protocol and its implementation. An independent DMC is responsible for period reviews of patient safety during the trial.

EUCLID was designed by the executive committee in cooperation with DCRI and the trial sponsor. Independent data analyses will be conducted by DCRI with validation by the trial sponsor. The executive committee has free and complete access to all trial data and will submit the results of the study for publication in a peer-reviewed medical journal.

The EUCLID study is supported by a research grant from AstraZeneca. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Discussion

Despite the increasing number of patients with lower extremity PAD [1], the evidence base for therapies aimed at improving both CV and limb outcomes is limited [29]. The current American College of Cardiology Foundation/American Heart Association/European Society of Cardiology guidelines for PAD recommend use of either aspirin or clopidogrel for reduction in CV events [4,5]. Unfortunately, these recommendations are based on the evaluation of effects in patients with PAD that were subgroups in larger trials. The EUCLID trial will define the role of antiplatelet therapy in patients with symptomatic PAD.

Therefore, as we considered a large trial aimed at patients with PAD, there were several important design considerations, including the population to be enrolled, the comparative therapies, management of patients during the trial, and the outcomes of interest.

Study population

Symptomatic patients with PAD are at high risk of CV events and require aggressive lifestyle and pharmacologic therapy for risk reduction. To address the paucity of data in PAD, the EUCLID trial includes the entire spectrum of symptomatic PAD, including abnormal ABI (ABI <0.80) or TBI (<0.60 with ABI >1.4), typical and atypical lower extremity symptoms, and rest pain with critical limb ischemia. In addition, EUCLID was designed to include

patients with or without revascularization (endovascular or surgical) or amputation.

Comparative antiplatelet therapy

When designing the study, different antiplatelet comparative groups were considered, including aspirin monotherapy, clopidogrel monotherapy, or dual antiplatelet therapy. The benefit of aspirin in the setting of PAD is far from certain. A meta-analysis including 9 trials of subjects with PAD did not detect a significant difference in CV events from aspirin versus placebo or control [6]. Clopidogrel monotherapy outperformed aspirin monotherapy in patients with prior MI, stroke, or PAD. In fact, the largest reduction in CV events from clopidogrel was observed in the PAD cohort, suggesting a greater effect of clopidogrel in the setting of PAD [10]. The CHARISMA trial failed to demonstrate a significant benefit of dual antiplatelet therapy in the overall trial [22] or in the PAD cohort [11]. Overall, this suggested that clopidogrel monotherapy was the most proven antiplatelet therapy strategy in subjects with PAD. To permit the most unbiased comparison of clopidogrel to ticagrelor, patients with 2 loss-of-function CYP2C19 alleles are excluded from the EUCLID trial.

Management during the study

EUCLID is designed as a pragmatic clinical trial. As such, usual or standard care is permitted, including endovascular or surgical interventions for treatment of symptomatic PAD. Although aspirin use is an exclusion criterion at the onset of the trial, the addition of aspirin is permitted in certain subjects (eg, incident CV event or revascularization) where dual antiplatelet therapy is recommended. For patients undergoing procedures, continuation of therapy was recommended, and a physician-supported helpline was available 24 hours a day, 7 days a week to answer clinical questions.

Limb end points

Clinically important limb events are being investigated and adjudicated as secondary end points of this trial. Because the population being studied is patients with symptomatic PAD, limb-specific end points are important to understand for this high-risk population. For that reason, this study is investigating ALI requiring hospitalization with the primary composite end point as the first major secondary end point. Other limb events being investigated include lower extremity revascularization, lower extremity clinical status (Rutherford and Fontaine stage), change in ABI (or TBI), amputation, and peripheral artery questionnaire. Moreover, the recently reported TRA2°P-TIMI 50 study compared vorapaxar, an oral antiplatelet agent targeting the protease-activated receptor-1 by thrombin, versus placebo in patients with prior MI, stroke, or PAD. Although vorapaxar did not reduce the primary composite end point in patients

with PAD, it significantly reduced ALI and peripheral revascularization [21]. These data support the hypothesis that potent antiplatelet therapy will reduce limb-specific events.

Summary

The EUCLID trial is investigating whether ticagrelor monotherapy versus clopidogrel monotherapy reduces major CV and limb-specific events in a broad representative population of patients with PAD.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ahj.2016.01.018>.

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