AstraZeneca

Amended Clinical Study Protocol

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A randomised, double-blind, parallel group, multicentre phase IIIb study to compare ticagrelor with clopidogrel treatment on the risk of cardiovascular death, myocardial infarction and ischaemic stroke in patients with established Peripheral Artery Disease (EUCLID – Examining Use of tiCagreLor In paD)

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	26 September 2013		
2	3 March 2015		

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PROTOCOL SYNOPSIS

A randomised, double-blind, parallel group, multicentre phase IIIb study to compare ticagrelor with clopidogrel treatment on the risk of cardiovascular death, myocardial infarction and ischaemic stroke in patients with established Peripheral Artery Disease (EUCLID – Examining Use of tiCagreLor In paD)

International Principal Investigator

William R. Hiatt

Study centre(s) and number of patients planned

This study will be conducted in approximately 950 investigational centres in approximately 25 countries worldwide. It is expected that approximately 13,500 patients will be randomised to study treatment.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2012	IIIb
Estimated date of last patient completed	Q3 2016	

Objectives

Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor vs. clopidogrel on the event rate of the composite of cardiovascular (CV) death, myocardial infarction (MI), and ischaemic stroke (defined as any stroke not demonstrated to be primarily haemorrhagic) in patients with established PAD (see definition Section 4.1). The primary efficacy variable is time from randomisation to first occurrence of any event in the composite of CV death, MI, and ischaemic stroke.

Secondary objectives

The secondary objectives (presented in hierarchical order – see Section 2.2 for details) of the study are to compare the effect of long-term treatment with ticagrelor vs. clopidogrel, in patients with established PAD (see definition Section 4.1):

1. Composite of CV death, MI, Ischemic Stroke and Acute Limb Ischemia (ALI) requiring hospitalization
2. CV death
3. MI
4. All-cause mortality
5. Composite of CV death, MI, and all-cause stroke (ischaemic or haemorrhagic)
6. Acute Limb Ischemia (ALI) requiring hospitalization
7. All Lower Extremity Revascularization
8. All revascularization procedures

Other objectives

Other objectives (see detail in Section 2.2.1) are exploratory with the purpose of comparing other possible long-term treatment effects of ticagrelor vs. clopidogrel, in patients with established PAD on:

- Net clinical benefit composed of primary outcome events and fatal or intracranial bleeding
- Net clinical benefit composed of primary outcome events and major bleeding
- Non-CV death
- Progression of the clinical/symptomatic status of the limb
- Progression of the haemodynamic status of the limb
- All amputations due to PAD
- Major amputation due to PAD
- Quality of life/functional status
- Primary efficacy and primary safety variable subgroup analysis (eg, clinical stage, prior MI, diabetes, hyperlipidemia, tobacco use, etc)
- CV-related hospitalisation
- Long term cost-effectiveness

Safety objectives

Non-serious adverse events (AEs) of interest (i.e., bleeding events, dyspnoea, renal impairment/increased creatinine, bradyarrhythmia, increased liver function tests, gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding, all malignancies excluding non-melanoma skin cancers), adverse events that are ongoing at the time of permanent discontinuation of study medication due to an adverse event (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug. The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared with clopidogrel in patients with established PAD after first dose of study medication. Bleeding events will be analyzed using the Thrombolysis in Myocardial Infarction Study Group (TIMI), Bleeding Academic Research Consortium (BARC) and International Society on Thrombosis and Haemostasis (ISTH)

definitions, and those used in the PLATO (PLATelet inhibition and patient Outcomes) study. Specific focus will be on:

- Time to first TIMI major bleeding event (primary safety objective)
- Time to first TIMI major or minor bleeding event
- Time to first PLATO major bleeding event
- Time to discontinuation of study medication due to any major bleeding event
- Evaluation of non-serious AEs of interest, DAEs and SAEs

Study design

This is a multicentre, randomised, double blind, double-dummy parallel group, endpoint driven phase IIIb study to assess the prevention of the primary and secondary endpoints and their individual components with ticagrelor given at 90 mg twice daily (bd) compared with clopidogrel given at 75 mg once daily (od) in patients with established PAD (as defined by the inclusion/exclusion criteria).

Target patient population

Male and female patients 50 years of age and over representing the spectrum of established PAD based upon objectively verified hemodynamic severity and symptomatic disease as defined by the inclusion criteria.

Study medication, dosage and mode of administration

Ticagrelor monotherapy: 90 mg given orally bd and corresponding placebo.

Comparator, dosage and mode of administration

Clopidogrel monotherapy: 75 mg given orally od and corresponding placebo.

Duration of treatment

Patients will receive either 90 mg ticagrelor orally bd and clopidogrel placebo in the morning, or 75 mg clopidogrel od (morning) and ticagrelor placebo bd. The patients will be followed for an anticipated minimum of 25 months and up to approximately 40 months. However, the actual duration of the study will be based on accrual of the predetermined number of events (1364) for the primary endpoint, and therefore the study may be shorter or longer than 40 months The anticipated median duration is 32 months.

Statistical methods

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI, and ischaemic stroke. The primary variable will be tested at 4.94% significance level (two-sided) to account for one 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, including centrally adjudicated events, using the Cox proportional hazards model with a factor for treatment group. The hazard ratio (HR) for ticagrelor vs. clopidogrel with 95% confidence intervals 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 the objectives. The confirmatory testing will continue at the 4.94% significance level until the first statistically non-significant difference of treatment effect in the sequence is observed.

The original study assumption was a 7% annual clopidogrel primary event rate and a HR of 0.85 over an 18 month accrual period and an anticipated 18 months of minimum follow-up would require randomization of approximately 13,500 patients to yield the required 1596 primary endpoint events, to provide 90% power at 4.94% significance level (adjusted for one interim analysis). The observed aggregate event rate is currently estimated to be approximately 4.1%, and to conclude the study in a timely manner with maintained data quality, the number of targeted primary events will be reduced to a minimum of 1364, which will provide 85% power at 4.94% significance level.

One interim analysis of efficacy by an independent Data Monitoring Committee (DMC) is planned when approximately 798 events has been observed.

If additional interim analyses of the primary efficacy outcome are conducted, the overall significance level will be adjusted according to an alpha spending function.

The same methods as described for the efficacy variables will be used to analyse the primary safety variables, time to bleeding events and time to discontinuation of treatment due to bleeding.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ABI	Ankle brachial index
ACC	American college of cardiology
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
AHA	American heart association
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
ASA	Acetyl salicylic acid; aspirin
AST	Aspartate aminotransferase
AZ	Astrazeneca pharmaceuticals
BARC	Bleeding academic research consortium
bd	Twice daily dosing
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAPRIE	A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events
CCU	Critical care unit
CEC	Clinical event adjudication committee
CHD	Coronary heart diseases
CI	Confidence interval
CK-MB	Creatinine kinase myocardial band
CLI	Critical limb ischaemia
CSA	Clinical study agreement

Abbreviation or special term	Explanation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CYP	Cytochrome
DAE	Adverse event(s) that are ongoing at the time of permanent discontinuation of study medication due to an adverse event.
DCRI	Duke clinical research institute
DMC	Data monitoring committee
EC	Ethics committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D	European quality of life-5 dimensions questionnaire
EQ-VAS	EQ-visual analogue scale
ESTV	End of study treatment visit
EUCLID	Examining Use of tiCagreLor In paD
FDA	Food and drug administration
FAS	Full analysis set
FU	Follow-up
GCP	Good clinical practice
GMP	Good manufacturing practice
GPIIb/IIIa	Glycoprotein IIB/IIIa receptor
GRand	AZ global randomisation system
HDL	High-density lipoprotein
HECON	Health economic
HR	Hazard ratio
IATA	International air transport association
IB	Investigator's brochure
ICF	Informed consent form

Abbreviation or special term	Explanation
ICH	International conference on harmonisation
ICU	Intensive care unit
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities in a particular country.
ISTH	International Society on Thrombosis and Haemostasis
ID	Identification
IPA	Inhibition of platelet aggregation
IRB	Institutional review board
ITT	Intent-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LBBB	Left bundle branch block
LDL	Low-density lipoprotein
LFT	Liver function test
LMWH	Low-molecular-weight heparin
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
MI	Myocardial infarction
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
Non serious Adverse Events of Interest	Includes safety topics such as bleeding events, dyspnoea, renal impairment/increased creatinine, bradyarrhythmia, increased LFTs, gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding, and all malignancies excluding non-melanoma skin cancers
NSAIDs	Non-steroidal anti-inflammatory drugs
OAE	Other significant adverse event (see definition in Section 11.2.1)
od	Once daily
PACD	Primary analysis censoring date
PAD	Peripheral artery disease
PAQ	Peripheral artery questionnaire

Abbreviation or special term	Explanation
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
Peri-event	In relation to concomitant medications this means all medications taken within 30 days prior to onset through resolution of the event
PLATO	Study acronym – a study of PLATelet inhibition and patient Outcomes
PPI	Proton pump inhibitor
PRO	Patient reported outcome
PTDV	Premature treatment discontinuation visit
RRR	Relative risk reduction
SAE	Serious adverse event (see definition in Section 6.4.2).
SCV	Study closure visit
SDV	Source data verification
SUSAR	Suspected unexpected serious adverse reactions
TBI	Toe brachial index
TIA	Transient ischaemic attack
TIMI	Thrombolysis in myocardial infarction study group
UFH	Unfractionated heparin
URL	Upper reference limit
WBDC	Web-based data capture

1. INTRODUCTION

1.1 Background

Atherosclerosis with associated arterial thrombosis is a systemic disease that can affect the cardiovascular, cerebrovascular and the peripheral artery circulations. Atherosclerosis of the arteries supplying the limbs is referred to as Peripheral artery disease (PAD). PAD can also include the carotid, the upper extremity, visceral and renal arteries. PAD arises from systemic atherosclerosis and is part of the cardiovascular disease continuum. Patients with PAD have a significant systemic atherosclerotic disease burden. Clinical manifestations associated with lower extremity PAD include decrements in functional capacity and quality of life, including loss of limb in the most severely affected patients. Patients with PAD also have elevated levels of platelet activity and are at substantial increased risk for platelet mediated adverse events, such as myocardial infarction (MI), ischaemic stroke, and cardiovascular (CV) death (Pande 2011).

Although medical advancements have been made in surgical and interventional techniques for the symptomatic management of PAD, there exists significant unmet medical need for advances in pharmacologic treatment. Lifestyle modification of risk factors such as smoking cessation, exercise, and weight loss as well as the medical management of risk factors such as diabetes, hypertension, and hyperlipidemia may slow the atherosclerotic disease progression. These interventions have not been shown to affect the symptoms or modify the disease process of PAD, except that exercise and certain drugs such as cilostazol increase the walking distance in claudicants.

Current treatment guidelines indicate that antiplatelet therapy reduces the risk of MI, stroke or vascular death in patients with PAD (ACCF/AHA Guidelines 2011,ESC 2011), recommending monotherapy with aspirin (ASA), in daily doses of 75-325 mg/day or clopidogrel 75mg a day as safe and effective antiplatelet therapy for patients with atherosclerosis. However, several recent studies in PAD patients (with those studies evaluating asymptomatic PAD) have not shown a benefit of aspirin (Belch 2008, Berger 2009, ESC 2011, Fowkes 2010, Hiatt 2008). Clopidogrel, an irreversible adenosine diphosphate (ADP) receptor antagonist, 75 mg/day, is also recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with coronary artery disease and atherosclerotic lower extremity PAD. The Clopidogrel versus aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study demonstrated significant benefit of clopidogrel monotherapy over ASA monotherapy in patients with recent MI, stroke, or symptomatic PAD over the 36-month study duration (CAPRIE Steering Committee 1996). The effect was mainly driven by the 24% relative risk reduction (RRR) seen in the composite endpoint in the PAD subgroup.

Since the CAPRIE study, several clinical studies have confirmed greater clinical efficacy of dual antiplatelet therapy with thienopyridine ($P2Y_{12}$ receptor blocker) and ASA versus ASA alone in patients with acute coronary syndromes (ACS) for up to a year of therapy (Yusuf 2001, Pande 2011, Sabatine 2005, Chen 2005). However, trials of patients with stable

atherosclerotic cardiovascular disease (including PAD) or subjects with multiple risk factors for atherosclerosis have not demonstrated superiority of dual antiplatelet therapy to monotherapy. ESC and ACC-AHA guidelines do not recommend dual antiplatelet therapy in PAD based on no additional benefit and an increased bleeding risk, while the ACC and AHA guidelines allows consideration of dual antiplatelet therapy for high-risk patients only (ACS or PCI).

Ticagrelor (AZD6140) is a reversibly-binding, potent, oral adenosine diphosphate $P2Y_{12}$ receptor blocker.

Recently, data from an AstraZeneca (AZ) study of platelet inhibition and patient outcomes (PLATO/D5130C05262), a Phase III pivotal efficacy and safety study with a duration of up to 12 months comparing ticagrelor 90 mg twice daily (bd) dosing to clopidogrel 75 mg once daily (od) dosing, following initial loading doses, in patients with ACS on ASA background, have demonstrated superiority of ticagrelor over clopidogrel in the prevention of fatal and non-fatal cardiovascular (CV) events. In PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint of CV death, MI, and stroke after ACS events (RRR 16%, absolute risk reduction (ARR) 1.9%; hazard ratio (HR) 0.84 [95% confidence interval {CI} 0.77, 0.92]; p = 0.0003). Furthermore, ticagrelor compared to clopidogrel decreased separately the rates of CV death (RRR 21%; ARR 1.1%; HR 0.79 [95% CI 0.69, 0.91]; p = 0.0013) and of MI (RRR 16%; ARR 1.1%; HR 0.84 [95% CI 0.75, 0.95]; p=0.0045), but not that of stroke. PLATO-defined 'Major bleeding' (primary safety endpoint) for ticagrelor did not differ significantly from that of clopidogrel (HR 1.04 [95% CI 0.95, 1.13]; p = 0.4336).

In summary, clopidogrel has, in the CAPRIE study, shown particular benefit in a PAD population, when compared with ASA alone. In the PLATO study, ticagrelor was shown to be superior to clopidogrel in an ACS population, when given in addition to background ASA. Since established lower extremity PAD is closely associated with atherosclerosis with vulnerable plaques and intravascular macro-and microthrombosis in other vascular territories, it is likely that more complete platelet inhibition may prevent additional atherothrombotic events in this population.

The current study is being conducted to determine whether treatment with ticagrelor, given as antiplatelet monotherapy, will reduce the incidence of atherothrombotic ischaemic events compared with treatment with clopidogrel monotherapy as measured by the composite of CV death MI, and ischaemic stroke in a population with established PAD. Further information regarding the background, pharmacological class, properties, and mechanism of action of ticagrelor can be found in the Investigator's Brochure (IB).

1.2 Research hypothesis

This study is designed to test the hypothesis that ticagrelor monotherapy when compared with clopidogrel monotherapy will reduce the incidence of atherothrombotic ischaemic events, as measured by the composite of CV death, MI, and ischaemic stroke in patients with established PAD.

1.3 Rationale for conducting this study

Previous studies have demonstrated the utility of low-dose ASA for secondary prevention of atherothrombotic events after appropriate risk stratification in patients with established coronary artery disease (CAD) and other atherosclerotic vascular disease (AHA 2006). As previously described, the CAPRIE study demonstrated that clopidogrel monotherapy was statistically better than ASA monotherapy for reducing the composite of cardiovascular death, MI, and stroke, in patients with stable atherosclerosis with the greatest benefit in the PAD subgroup (CAPRIE Steering Committee 1996). The risk level of ischaemic events in patients with PAD continues to be very high yet stable during the remaining lifetime.

Aspirin and clopidogrel are each recommended in the guidelines for prophylaxis as monotherapy in patients with PAD (Norgren (TASC II) 2007, Hirsch 2006). Within the PAD guidelines, treatment duration for either clopidogrel or ASA remains unspecified, in contrast to the case for ACS and related diseases. Aspirin plus clopidogrel in combination did not improve outcomes among a patient population with stable coronary, cerebrovascular or peripheral artery disease or multiple atherosclerotic risk factors. Although the subset of patients showed fewer MIs with dual therapy, there was no benefit on the primary endpoint of MI, stroke, and vascular death and the PAD group also demonstrated increased bleeding (Bhatt 2007, Wang 2007, Cacoub 2009).

Ticagrelor 90 mg bd has greater platelet inhibition than clopidogrel but, unlike clopidogrel, ticagrelor does not require metabolic activation. As a result, ticagrelor provides more consistent inter-patient antiplatelet effect. PLATO demonstrated a 16% RRR of ticagrelor 90 mg bd versus clopidogrel in major adverse CV events following ACS, a 21% RRR in CV mortality, and a numerical 22% RRR in all-cause mortality (Wallentin 2009). Ticagrelor's benefits should translate to continued protection of patients with established PAD. The selection of CV death and all-cause mortality as secondary endpoints in this study allows further exploration of the effects of ticagrelor on mortality in patients with high cardiovascular risk.

1.4 Benefit/risk and ethical assessment

Current American Heart Association (AHA)/American College of Cardiology (ACC) and transatlantic multi-society guidelines recommend ASA or clopidogrel for patients with established PAD (AHA 2006, Norgren (TASC II) 2007, ACCF/AHA Guidelines 2011,ESC 2011). In the PLATO study, ticagrelor 90 mg bd in combination with ASA was shown to reduce several CV endpoints in patients with ACS and a history of PAD. In the subset of patients with a history of PAD at baseline (N = 566 ticagrelor, N = 578 clopidogrel), ticagrelor numerically reduced the composite endpoint of CV death, MI, and stroke compared to clopidogrel; HR 0.85 (0.64 – 1.11).

ESC Guidelines for PAD indicate clopidogrel monotherapy instead of aspirin for patients with stable CAD (class IIa, Level B).

More than 11,000 healthy subjects or patients have been exposed to ticagrelor in the completed phase I, II and III studies and the overall conclusion based on these studies is that ticagrelor has generally been well tolerated. Despite greater inhibition of platelet aggregation (IPA) with ticagrelor, results from the PLATO study showed that PLATO Major bleeding with ticagrelor did not differ from that with clopidogrel. Although the total Major bleeding did not differ between ticagrelor and clopidogrel in the PLATO study, non-procedural PLATO defined 'Total-Major bleeding' rates were significantly greater with ticagrelor compared to clopidogrel (3.1% vs. 2.3%, HR 1.31 [95% CI 1.08, 1.60]; p = 0.006). This difference between ticagrelor and clopidogrel in non-procedural bleeding diminished as bleeding categories became more severe. Thus, there was no difference between treatment groups in the 'Major Fatal/Life-threatening' and 'Fatal non-procedural' bleeds. Adverse events (AEs) observed in patients treated with ticagrelor, other than bleeding, include dyspnoea (a feeling of breathlessness), minimal increases in serum creatinine (difference of 1-2 μM or 0.01 to 0.02 mg/dL in mean creatinine values when comparing with clopidogrel-treated patients), increases in serum uric acid concentrations, and ventricular pauses that were largely asymptomatic. None of these events is considered to pose a significant risk as they can be adequately handled in the clinical situation.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor vs. clopidogrel on the event rate of the composite of cardiovascular (CV) death, myocardial infarction (MI), and ischaemic stroke (defined as any stroke not demonstrated to be primarily haemorrhagic) in patients with established PAD (see definition Section 4.1). The primary efficacy variable is time from randomisation to first occurrence of any event in the composite of CV death, MI, and ischaemic stroke.

2.2 Secondary objectives

The secondary objectives (presented in hierarchical order) of the study are to compare the effect of long-term treatment with ticagrelor vs. clopidogrel, in patients with established PAD (see definition Section 4.1) on:

- The event rate of cardiovascular death (CV Death) , Myocardial infarction (MI), Ischemic Stroke, and Acute Limb Ischemia (ALI). The efficacy variable is time from randomization to first occurrence of any event in the composite of CV Death, MI, Ischemic Stroke and ALI.

- The event rate of CV death. The efficacy variable is time from randomisation to occurrence of CV death.

- The event rate of MI. The efficacy variable is time from randomisation to occurrence of MI.

- the event rate of all-cause mortality. The efficacy variable is time from randomisation to all-cause mortality.

- The event rate of CV death, MI, and all-cause stroke (ischaemic or haemorrhagic). The efficacy variable is time from randomisation to CV death, MI, and all-cause stroke (ischaemic or haemorrhagic).

- The event rate of ALI. The efficacy variable is time from randomisation to occurrence of ALI.

- The event rate of Lower Extremity Revascularization. The efficacy variable is time from randomisation to occurrence of Lower Exetremity Revascularization

- The event rate of all revascularization (coronary and periphera [limb, mesenteric, renal, carotid and other]). The efficacy variable is time from randomisation to occurrence of any revascularization

2.2.1 Other objectives

Other objectives are exploratory with the purpose of comparing other possible long-term treatment effects of ticagrelor vs. clopidogrel in patients with established PAD on:

- Net clinical benefit evaluated by
  a) The variable is time from randomisation to first occurrence of any event in the following composite of all-cause mortality, MI, ischaemic stroke, ALI or major amputation caused by PAD, and fatal bleeding or intracranial bleeding.
  b) The variable is time from randomisation to first occurrence of any event in the following composite of all-cause mortality, MI, ischaemic stroke, ALI or major amputation caused by PAD, and TIMI major bleeding.
- the event rate of non-CV death. The efficacy variable is time from randomisation to occurrence of non-CV death.
- the progression of the clinical/symptomatic status of the limb by changes in clinical stage (Rutherford and Fontaine stage).
- The event rate of all amputations. The efficacy variable is time from randomization to occurrence of all amputations caused by PAD
- the event rate of major amputation caused by PAD. The efficacy variable is time from randomisation to occurrence of major amputation caused by PAD.

- the impact on quality of life by collecting health related quality of life data using the Peripheral Artery Questionnaire (PAQ). The PAQ instrument will be administered at all clinics in countries where a validated form is available in local language.
- the primary efficacy and primary safety variable in subgroups of patients with established risk factors for PAD (eg, clinical stage, prior MI, diabetes, hyperlipidemia, tobacco use, etc).
- the event rate of CV-related hospitalisation (including all-cause death, MI, ischaemic stroke, lower extremity revascularisation, major amputation due to PAD, transient ischaemia attack (TIA), coronary revascularisation or unstable angina). The efficacy variable is a) total CV hospital days, and b) time from randomisation to first occurrence of any of these events. Any individual component not already evaluated will also be examined in an analogous manner.
- the within study cost consequences and the long term cost-effectiveness of ticagrelor vs. clopidogrel to support health technology assessment. Information will be collected on health care utilization associated with hospitalisations, rehabilitation and long-term care in all patients. Utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) will be collected at all clinics in countries where a validated form is available in the local language.

2.3 Safety objective

Non-serious AEs of interest (ie, bleeding events, dyspnoea, renal impairment/increased creatinine, bradyarrhythmia, increased liver function tests [LFTs], gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding, all malignancies excluding non-melanoma skin cancers), adverse events that are ongoing at the time of permanent discontinuation of study medication due to an adverse event (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug. The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to clopidogrel in patients with established PAD. Bleeding events will be analyzed using the Thrombolysis in Myocardial Infarction Study Group (TIMI), PLATO, Bleeding Academic Research Consortium (BARC) and International Society of Thrombosis and Haemostasis (ISTH) definitions. Specific focus will be on:

- Time to first TIMI major bleeding event following the first dose of study medication (primary safety objective)
- Time to first TIMI major or minor bleeding event
- Time to first PLATO major bleeding event

- Time to permanent discontinuation of study medication due to any major bleeding event

- Evaluation of non-serious AEs of interest, DAEs and SAEs

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subject to a peer review and approval by the Executive Committee and the Data Monitoring Committee according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a multicentre, randomised, double blind, double-dummy, parallel group, endpoint driven phase IIIb study to assess the prevention of atherothrombotic events with ticagrelor 90 mg bd compared to clopidogrel 75 mg od in patients with established PAD. The study design is shown in Figure 1.

The study will be designed, directed and published by an Executive Committee (see Section 5.10.1.1). The following additional committees will be selected; an independent safety Data Monitoring Committee (DMC) (see Section 12.4.2), a blinded independent Clinical Event adjudication Committee (CEC) (see Section 12.4.1), an International Steering Committee (see Section 5.10.1.2), and an Operations Committee (see Section 5.10.1.3).

Duration of the study

The anticipated duration of the study is approximately 40 months, including an anticipated enrolment period of 15 months and follow-up period of 25 months. However, the actual duration of the study will be based on accrual of the predetermined number of events (1364) for the primary endpoint, and therefore the study may be shorter or longer than 40 months. Any decision to increase or decrease patient numbers or extend or shorten treatment duration will be based on blinded event rate data. The Executive Committee of the trial will monitor the aggregate blinded event rate and may change the sample size or duration of follow-up to achieve the planned target number of events, in consultation with the sponsor and, as needed, the DMC.

The study plan, including enrolment/randomisation and protocol visits, is outlined in Table 1. If it is necessary to prolong the study in order to accrue the predetermined number of the primary endpoint events, visits and assessments will continue at the same frequency (ie, every 6 months).

Enrolment and randomisation

Male and female patients 50 years of age and over with established PAD, fulfilling all of the inclusion criteria (see Section 4.1) and none of the exclusion criteria (see Section 4.2) can be randomised.

The study will enrol symptomatic patients representative of the PAD disease spectrum.

Approximately 13,500 patients at approximately 950 study centres will be randomised (1:1) to receive either ticagrelor or clopidogrel monotherapy. The sample size is based on anticipated event rates that are related to the clinical stage of the disease. In an effort to achieve an appropriate claudication to critical limb ischaemia (CLI) final distribution ratio, the Executive Committee will monitor the Fontaine class (clinical stage) (Norgren (TASC II) 2007) and primary event rates and may cap enrolment to a particular subgroup based on the overall distribution and event rates. The Executive Committee will also monitor the proportion of patients enrolled with a prior history of MI and may cap enrolment on this subgroup as well.

Protocol Visits

Patients will return approximately every 6 months as outlined in Figure 1 and Table 1, for assessment of events related to the objectives of the study including efficacy, tolerability and safety. Assessment of treatment compliance and provision of study medication will be done at these visits. When visits are performed every 6 months, phone contacts will additionally be performed at a 3-month interval in between regular visits. The Investigator/study centre personnel will record non-serious AEs of interest (if any), DAEs, SAEs (if any), suspected clinical events (if any), study medication status, and use of concomitant medication. An unscheduled visit may be conducted as a result of the phone contact (eg, to follow-up on suspected clinical events).

Unscheduled visits

Unscheduled visits or phone contacts may be performed for event follow-up or early discontinuation of study medication.

Premature Treatment Discontinuation Visit (PTDV)

Patients who prematurely and/or permanently discontinued treatment with study medication but agreed to continue protocol visits should return for a PTDV, which will be done as soon as possible but no later than 15 days after prematurely discontinuing treatment with study medication. The PTDV will assess the same factors as the ESTV, with the only difference that patients who discontinue treatment early will be eligible for a PTDV.

End of Study Treatment Visit (ESTV)

When the predetermined number of primary events is anticipated, the following will occur:

- The Primary Analysis Censoring Date (PACD) will be declared by the Executive Committee
- All centre Investigators will receive communication to complete study visits as follows:
  - All randomised patients should return for their ESTV as soon as possible but not later than 60 days after the Primary Analysis Censoring Date (PACD).

- Study patients will be instructed to transition from study medication to accepted antiplatelet therapy per current practice guidelines and standards.

Study Closure Visit (SCV)

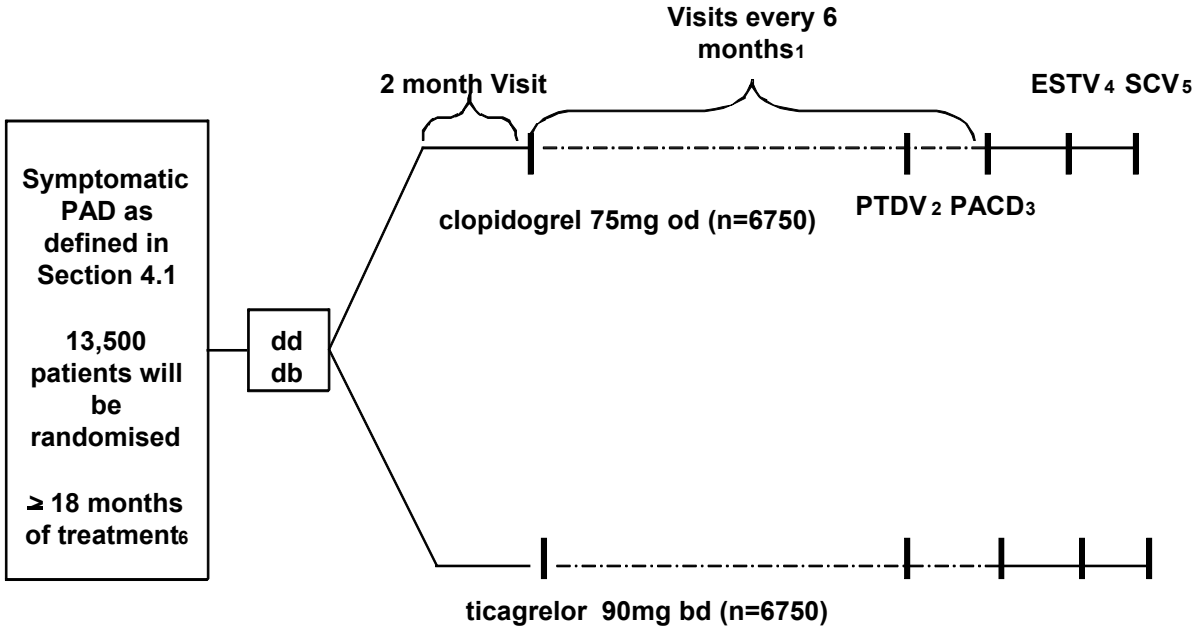
- All randomised patients should return for their SCV, 35 days ± 5 days, after their ESTV.

- All patients who prematurely and/or permanently discontinued treatment with study medication should return for the SCV as soon as possible but not later than 60 days after the PACD.

- Patients who are not attending scheduled visits when PACD is declared will be contacted to schedule their SCV as soon as possible but not later than 60 days after PACD, for assessment of as many endpoints in the trial as possible (ie, health or vital status as per agreement at a minimum) in person, by telephone, by checking medical records or by collecting information from publicly available sources. It is strongly recommended that all patients attend their SCV in person.

For further details on procedures for discontinuing patients from study medication, refer to Section 5.8, and for the rare patient who must withdraw from study (study medication and visit assessments) refer to Section 5.9.

Figure 1 Study Flow Chart



dd = double dummy, db = double blind, PTDV = Premature Treatment Discontinuation Visit, PACD = Primary Analysis Censoring Date, ESTV = End of Study Treatment Visit, SCV = Study Closure Visit, od = once daily dosing, bd = twice daily dosing

1 Telephone follow-up will additionally be performed at a 3-month interval in between regular visits. Non-serious AEs of interest, DAEs, SAEs, suspected clinical events, study medication and concomitant medication status will be recorded. An unscheduled visit may be conducted as a result of the phone contact.
2 The Premature Treatment Discontinuation Visit (PTDV) is only done for patients who prematurely and/or permanently stop study medication.
3 The primary analysis censoring date (PACD) is time point in which the Executive Committee determines the number of events has been reached and study closure activities may begin.
4 The end of study treatment visit (ESTV) should occur as soon as possible but not later than 60 days after PACD.
5 The study closure visit (SCV) should occur within 35 days ± 5 days from the last dose of study medication following PACD.
6 Study period will be approximately 18 months recruitment and an anticipated minimum of 18 months follow-up. The actual study period will be determined when the projected number of pre-specified primary events has been reached.

Table 1 Study Plan

	Visit 1	Visit 2	Visit 3	Visits 4-X [a]	Premature Treatment Discontinuation Visit (PTDV)	End of Study Treatment Visit (ESTV)	Study Closure Visit (SCV)
Assessment	**Enrolment ≤ 30 days prior to randomisation**	**Randomisation Day 0**	**2 months from randomisation ± 7d**	**6, 12, 18, 24, 30, 36 months from randomisation ± 7d**	**No more than 15 days from last dose of study medication [b]**	**Within 60 days from Primary Analysis Censoring Date (PACD) [c]**	**See footnote [d]**
Signed Informed Consent	√						
Inclusion & Exclusion criteria	√	√					
Relevant medical and surgical history		√					
Demographics	√						
Ankle Brachial Index (ABI) or Toe Brachial Index (TBI)[f]	√ [e]	√ [e]		√ [e]	√	√	
CYP2C19 polymorphism (central lab)	√						
Electrocardiogram (ECG)		√					
Vital Signs		√	√	√	√	√	
Targeted Physical Examination		√					
Clinical chemistry & Haematology (local lab)	√				√	√	

	Visit 1	Visit 2	Visit 3	Visits 4-X [a]	Premature Treatment Discontinuation Visit (PTDV)	End of Study Treatment Visit (ESTV)	Study Closure Visit (SCV)
Urinalysis (local lab)	√						
Urine pregnancy test (local lab) [g]	√						
EQ-5D questionnaire		√		√ [h]	√	√	
PAQ questionnaire		√		√ [h]	√	√	
Hospitalisation information		√	√	√	√	√	√
Rehabilitation information		√	√	√	√	√	√
Long-term care information		√	√	√	√	√	√
Dispense Study Medication		√	√	√			
Return Study Medication			√	√	√	√	
Compliance/ Study Medication accountability			√	√	√	√	
Current Medications	√	√	√	√	√	√	√
Non-serious AEs of interest, DAEs, SAEs, and Endpoints	√ [i]	√ [i]	√	√	√	√	√

a The study is event driven and the number of visits will depend on when the pre-estimated number of primary events has been reached. If study continues > 36 months, visits will continue every six months. Telephone follow-up will additionally be performed at a 3-month interval in between regular visits.
b The Premature Treatment Discontinuation visit (PTDV) is only done for patients who prematurely and/or permanently stop study medication.
c The End of Study Treatment Visit (ESTV) should occur as soon as possible but not later than 60 days after the Primary Analysis Censoring date (PACD).
d All randomised patients should return for their SCV, 35 days ± 5 days, after their ESTV; All patients who prematurely and/or permanently discontinued treatment with study medication should return for the SCV as soon as possible but not later than 60 days after the PACD. Patients who are not attending scheduled visits when PACD is declared will be contacted to schedule their SCV as soon as possible but not later than 60 days after the PACD, for

assessment of health status or vital status as per agreement, ie, in person, by telephone, by checking medical records or by collecting information from publicly available sources**. It is strongly recommended that all patients attend their SCV in person.**

e Two ABI/TBI measurements must be taken (Visit 1 and Visit 2) to determine eligibility for the study for patients enrolling under ABI criteria. One ABI/TBI measurement must be taken at Visit 1 for those entering under the revascularization criteria. For all patients, ABI is then measured at Visit 4 and ESTV. The ABI measurement at Visit 1must be ≤ 0.80 and the ABI measurement at Visit 2 must be ≤ 0.85. If ABI is ≥ 1.40 at Visit 1 then TBI must be taken at Visit 1 and Visit 2 for eligibility. The TBI measurement at Visit 1 must be ≤ 0.60 and the TBI measurement at Visit 2 must be ≤ 0.65. The measurement ankle vessel and limb used at V1 and V2 should be the one that is used for all subsequent visits. Subsequent measurements will occur at the 6-month visit and PTDV/ESTV. The V1 and V2 ABI/TBI measurement for the first three subjects at each site will be assessed for quality.

f Photoplethysmographic (PPG) signal is acceptable method of assessment of TBI.

g Only in women of child-bearing potential.

h EQ-5D and PAQ will be collected at V2 then annually starting at the 12 month visit, and PTDV/ESTVs.

i SAEs will be recorded from the time of informed consent, Non-serious AEs of interest, DAEs and endpoints will be collected from time of randomisation.

3.2 Rationale for study design, doses and control groups

Rationale for study design

This is a randomised phase IIIb, double blind, double-dummy, parallel group, endpoint driven study.

Randomisation and double blinding will minimise potential bias. Parallel group design was chosen because a crossover study cannot assess long-term outcomes. This multicentre study will be conducted in numerous geographic regions to provide a wide applicability of results.

The target minimum treatment duration of 18 months has been selected with the goal of demonstrating long-term efficacy and safety, as life-long anti-platelet treatment is strongly recommended in this population (AHA 2006). The actual study event accrual may lead to less than an 18 month minimum duration for those subjects last-randomised (see section 12.2.4).

Patients and Choice of endpoints

The target population will be patients with PAD who present clinically with lower extremity symptoms or who had previously undergone revascularization for symptomatic PAD. Patients may have a prior history of symptomatic CAD (ie, prior myocardial infarction, acute coronary syndrome or coronary revascularization), however, symptomatic PAD will be their main clinical presentation. In two recent large placebo-controlled studies of aspirin (AAA [Fowkes 2010] and POPADAD [Belch 2008]) in asymptomatic subjects with an abnormal ABI, there was no treatment effect. However, prior studies including patients with lower extremity symptoms demonstrated a response to a variety of other antiplatelet therapies (Antithrombic Trialists' Collaboration 2002, ACCF/AHA Guidelines 2011,ESC 2011). Therefore, this study will enrol patients with symptoms of PAD or who had previously undergone revascularization for symptomatic PAD.

For patients qualifying for enrolment via the ABI criteria, the entry ABI measurement of ≤ 0.80 was chosen to improve the specificity of the ABI to ensure that patients enrolled actually have PAD (given the 0.10 test-retest variation, an ABI of 0.80 ensures that the upper bound would be ≤ 0.90). Hence, for these patients, the ABI at the Randomisation Visit must be ≤ 0.85 to ensure that all patients enrolled have substantial haemodynamic evidence of PAD.

Alternatively, patients may qualify for enrolment by having prior lower extremity revascularization for symptomatic and haemodynamically significant PAD greater than 30 days prior to randomisation, irrespective of present leg symptoms and the ABI or TBI at the time of study screening.

Age 50 was chosen because non-atherosclerotic occlusive disease is more common in younger patients. The target pathophysiology of antiplatelet therapy is systemic atherosclerosis.

In CAPRIE, the PAD subgroup in particular responded well to clopidogrel relative to aspirin. Prior studies with ticlopidine also demonstrated benefit in the PAD population. Thus there is good rationale that PAD patients respond well to platelet ADP P2Y receptor antagonists.

Given the superiority of ticagrelor over clopidogrel in PLATO, and the positive PAD subgroup findings in that study, the investigators believe that ticagrelor monotherapy will also provide advantages over clopidogrel in the current study.

This is a monotherapy study in a high-risk patient population with stable atherosclerosis. This population differs from the ACS patients studied in PLATO and from the ongoing PEGASUS study (comparing ticagrelor with placebo on background ASA in patients with a history of MI). PEGASUS specifically excluded from participation patients with PAD. The population of PAD patients entering the study must be candidates for antiplatelet monotherapy as per the AHA/ACCF/PAD Guidelines issued 2011 (ACCF/AHA Guidelines 2011).

Clopidogrel, in the CAPRIE study, has shown particular benefit with respect to an overall reduction in vascular events in a PAD population, when compared to ASA alone (CAPRIE Steering Committee 1996). In the PLATO study, ticagrelor was superior to clopidogrel for the prevention of subsequent thrombotic events in an ACS population, when given on top of ASA. Since established PAD is a manifestation of symptomatic atherosclerosis with vulnerable plaques and intravascular macro- and microthrombosis, it stands to reason that more complete platelet inhibition may prevent additional atherothrombotic events in this population. Patients in this study will represent the spectrum of peripheral vascular occlusive disease; with objectively verified hemodynamic severity, symptomatic disease, and associated CV risk factors.

Patients with a prior myocardial infarction may participate in the trial. Guidelines worldwide specify lifelong therapy with aspirin or a more potent antiplatelet medication, such as clopidogrel. ESC guidelines (ESC 2011) specify that patients with PAD who also have clinical evidence of coronary artery disease benefit from clopidogrel monotherapy as much as from aspirin alone. This trial will provide monotherapy with clopidogrel or the more potent antiplatelet agent ticagrelor to all patients taking study medication, consistent with guidelines for patients with both PAD and PAD with coronary artery disease.

Choice of Primary Composite Endpoint

The primary endpoint composite of CV death, MI, and ischaemic stroke was chosen to best reflect the enhanced efficacy of more complete platelet inhibition. In the PLATO study, ticagrelor decreased separately the rates of CV death and of MI. No statistically significant difference was observed between ticagrelor and clopidogrel for the efficacy component of stroke. However as ischaemic stroke is an important efficacy measure of clinical consequence, it is a part of the primary endpoint composite. In addition, the CAPRIE study, which forms the basis for use of this trial's comparator, monotherapy clopidogrel, used the composite endpoint of myocardial infarction, ischaemic stroke, and CV death. A sensitivity analysis of the current trial will evaluate the composite endpoint of myocardial infarction, all strokes, and CV death.

Dose regimens

Ticagrelor 90 mg bd was selected as a dose to be tested in this study based on available data. The dose was well tolerated and showed high and consistent levels of IPA in Phase 2 studies,

with an acceptable safety profile. The phase III study (PLATO) showed a positive benefit to risk balance with this dose.

Clopidogrel was chosen as the active comparator, as the CAPRIE study results supported the superiority of clopidogrel over ASA and has resulted in clopidogrel being listed as alternative monotherapy to ASA in the current guidelines for the management of PAD. The clopidogrel 75 mg od dose was selected since it is the approved maintenance dose in clinical practice. Concomitant low dose ASA (defined as ≤ 150 mg od) after enrolment is allowed to treat emergent conditions only if mandated by current practice guidelines (see Section 5.6.1). Based on pharmacokinetic data indicating poor metabolism of clopidogrel to its active metabolite may decrease the clinical benefit of clopidogrel, all candidate subjects will undergo genotype determination for the cytochrome P450 enzyme 2C19; those with 2 copies of loss of function alleles will not participate in the trial (exclusion item #1).

The dosage of ticagrelor was chosen based on pharmacodynamic (PD), IPA, efficacy, and safety information gained from phase II studies, including Study D5130C00008 (DISPERSE), which demonstrated that the 90 mg dose was well tolerated and showed high and consistent levels of IPA with an acceptable safety profile.

The efficacy and safety of the 90 mg bd dose was established in PLATO, in which ticagrelor showed superiority to clopidogrel 75 mg od in reducing the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events, with a RRR of 16%. Overall, ticagrelor at 90 mg bd was associated with a positive benefit:risk profile in PLATO.

Despite greater inhibition of platelet aggregation (IPA) with ticagrelor, results from the PLATO study showed that PLATO Major bleeding with ticagrelor did not differ from that with clopidogrel. Although the total Major bleeding did not differ between ticagrelor and clopidogrel in the PLATO study, non-procedural PLATO defined ‘Total-Major bleeding’ rates were significantly greater with ticagrelor compared to clopidogrel (3.1% vs. 2.3%, HR 1.31 [95% CI 1.08, 1.60]; p = 0.006). This difference between ticagrelor and clopidogrel in non-procedural bleeding diminished as bleeding categories became more severe. Thus, there was no difference between treatment groups in the ‘Major Fatal/Life-threatening’ and ‘Fatal non-procedural’ bleeds.

Available data from phase I and II studies do not support exposing patients to a higher ticagrelor dose. The higher dose would achieve minimally greater IPA, with a predicted minimal impact on the primary efficacy composite outcome; however, it would do so at the expense of a small increase in Major bleeding. Based on these findings together, the investigators do not find benefit to risk justification to expose patients to doses greater than 90 mg bd.

Available data also do not support exposing patients to a lower ticagrelor dose. The lower dose would result in a 2- to 3-times increase in variability in IPA and substantially lower mean trough IPA, similar to that achieved with clopidogrel.

Study D5135C00001 (PAD) is a monotherapy study that will enrol patients at high risk for experiencing CV events; the study will include patients with known or unknown concomitant CAD. Dual therapy that includes low-dose ASA (≤ 150 mg od) will not be permitted at baseline for this study population, and will be initiated only if a patient develops an indication during the study (eg, ACS event, percutaneous coronary intervention [PCI] or peripheral revascularisation).

Patients already enrolled in the study who develop an indication for dual antiplatelet therapy, defined as having an ACS event (per AHA definition), a PCI, or peripheral revascularisation can continue with blinded study medication (ticagrelor or clopidogrel) + low-dose ASA (defined as ≤ 150 mg od) for the duration required by appropriate guidelines (Yusuf 2001, Anderson 2007, Bassand 2007, King 2008). A single loading dose of ASA, at any dose, is allowed. This approach allows patients to receive appropriate antiplatelet care while maintaining the integrity of the blind and allowing long-term safety experience with ticagrelor to be obtained.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record of patients who entered pre-study screening. Screening data will be captured in the IVRS/IWRS.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. However, a patient who was previously deemed a screen failure may become eligible for enrolment, if due to their disease progression and/or clinical changes, they meet all of the inclusion criteria and none of the exclusion criteria for this study at a later time. If after randomisation, a concern regarding inclusion or exclusion criteria is identified, investigators will discuss the findings with the EUCLID Study Physician via the clinical hotline.

Referring physicians as well as specialists (ie, geriatricians, angiologists, cardiologists, vascular surgeons, vascular medicine physicians and other physicians who take care of patients suffering from established PAD) can serve as investigators in this study. It is important to note that patients may be chosen from lists and records describing patients who have undergone interventions for established PAD or who have been candidates for such interventions. In all cases, it is important to describe, in the IVRS/IWRS, those not being randomised and the reasons therein.

A small number of patients may have a cytochrome CYP2C19 polymorphism for 2 loss-of-function alleles, categorizing them as “poor metabolisers” of clopidogrel to its active form. Therefore all patients will have CYP2C19 polymorphism samples collected at the enrolment visit. Poor metabolisers so identified will be excluded from randomisation.

Both PAD and CAD represent manifestations of atherosclerotic cardiovascular disease. For this reason, patients with symptomatic PAD may also have symptomatic CAD. These patients cannot be excluded from the trial whilst keeping the remaining cohort representative of the

PAD population. For this reason, patients with both PAD and CAD may participate. The trial will take special measures to address a concern that patients with PAD and a prior myocardial infarction (those studied in PLATO or PEGASUS) might account for a disproportionate share of the treatment effect. First, the investigator will specify each patient's status with respect to prior MI at randomisation, with prior MI defined at medical history intake, with or without source documentation of ECG or biomarker evidence. Second, the Executive Committee will monitor the proportion of patients with prior MI periodically during the enrolment period to ensure that the treatment effect in both subgroups can be estimated with appropriate precision.

4.1 Inclusion criteria

To ensure enrolment of patients representative of the PAD disease spectrum, patients will be included based upon objectively verified arterial burden and symptomatic disease.

For inclusion in the study patients should fulfil the following criteria at Visit 1.

1. Male and female patients ≥ 50 years of age

2. Symptomatic lower extremity PAD defined by:

   Symptoms at the time of screening including classic claudication, other exertional leg discomfort associated with physical limitations from PAD, ischaemic rest pain, ischaemic ulcers, or gangrene **AND**

   Ankle brachial index (ABI) measurement of ≤ 0.80 at Visit 1. The ABI must be ≤ 0.85 at Visit 2. If ABI is ≥ 1.40 then the toe brachial index (TBI) must be ≤ 0.60 at Visit 1 and the TBI must be ≤ 0.65 at Visit 2.

   OR

   Prior lower extremity revascularization for symptomatic and haemodynamically significant PAD greater than 30 days prior to randomisation, irrespective of present leg symptoms and the ABI or TBI at the time of study screening

3. Written informed consent prior to any study specific procedures.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Poor metabolizer status for CYP2C19, defined as possessing genotype consisting of 2 loss of function alleles.

2. Hypersensitivity to clopidogrel or ticagrelor

3. Patients requiring dual anti-platelet therapy at study entry

4. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin or long-term treatment with fondaparinux

5. Planned (and judged necessary) use of ticlopidine, prasugrel, aspirin or dipyridamole

6. Planned (and judged necessary) use of omeprazole or esomeprazole. *Note – the use of other proton pump inhibitors is permitted.*

7. 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 non-steroidal anti-inflammatory drugs [NSAIDs])

8. Life expectancy < 6 months based on investigator's judgement

9. Planned revascularisation (surgical or endovascular) in any vascular territory within the next 3 months

10. Planned major amputation due to PAD within the next 3 months or major amputation due to PAD within the last 30 days

11. Patients who have suffered a stroke during the past 3 months

12. Dementia likely to jeopardise understanding of information pertinent to study conduct or compliance to study procedures

13. Severe hypertension that may put the patient at risk

14. Patients considered to be at risk of bradycardic events (e.g., known sick sinus syndrome or second or third degree atrioventricular [AV)] block) unless already treated with a permanent pacemaker

15. Known severe liver disease (eg, ascites and/or clinical signs of coagulopathy)

16. Renal failure requiring dialysis

17. A clinically important bleeding diathesis, haemostatic or coagulation disorder or systemic bleeding

18. History of previous intracranial bleed at any time, gastrointestinal bleed within the past 6 months, or major surgery within 30 days (if the surgical wound is judged to be associated with an increased risk of bleeding)

19. Clinically important thrombocytopenia or neutropenia

20. Females of child-bearing potential (ie, those who are not chemically or surgically sterilised or who are not post-menopause) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR females who have a positive pregnancy test at Visit 1.

21. Concern for inability of the patient to comply with study procedures and/or follow-up (eg, alcohol or drug abuse)

22. Previous randomisation in the present study

23. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study centre)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

There are no specific dietary or activity restrictions other than those typical for this patient population.

Patients should not donate blood or bone marrow at any time during the study period.

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment and randomisation

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2.

3. Assign (using the Interactive Voice Response System/ Interactive Web Response System [IVRS/IWRS], see Section 5.2.1) each potential patient a unique enrolment number, beginning with ‘E#’.

4. Assign each enrolled patient a unique randomisation code (patient number) obtained from IVRS/IWRS after meeting all eligibility requirements.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be re-used.

5.2.1 Procedures for randomisation

Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two treatment arms. Approximately 13,500 patients will be randomised in this study.

For all patients who fulfill all the eligibility requirements, the investigator will access the IVRS/IWRS. The IVRS/IWRS will allocate a randomisation code and provide the investigator with unique treatment kit identification (ID) numbers for that patient for the Visit 2 supply of medication. Following randomisation, the first dose of study medication will be administered to the patient as soon as possible.

The randomisation codes will be computer generated by AstraZeneca R&D using the AZ Global Randomisation (GRand) system and loaded into the IVRS/IWRS database.

5.3 Procedures for handling patients incorrectly enrolled or randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

If a patient does not meet the selection criteria but is randomised in error or incorrectly started on treatment, a discussion should occur (clinical Hotline, email, telephone, etc.) between the EUCLID Study Clinical Team and/or DCRI Clinical Team and the Investigator regarding whether to continue or discontinue the patient from treatment. Consistent with Intent-To-Treat (ITT) principles, all randomised patients should continue to be followed in the study (i.e. attend protocol visits) and, unless treatment would be harmful, patients should continue to receive study medication. Every effort must be made to ascertain all efficiacy and safety events throughout the conduct of the study.

The EUCLID Study and DCRI Clinical teams are to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped but will continue with study assessments or telephone follow-up.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The treatment allocation in this study will be double-blind, and double-dummy. The tablets of ticagrelor (90 mg) and clopidogrel (75 mg) to be administered in the study have different appearances, see Table 2. To ensure the blinding of the treatments, matching ticagrelor placebo tablets and clopidogrel placebo tablets will be provided and given in a double-dummy fashion. Each pack will be labelled with a unique kit ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator or patient.

Investigators may not undertake laboratory or bedside tests that measure platelet activity (i.e. IPA, Verify Now, etc) during the study, unless it is directly related to participation in an approved sub study, where data were appropriately coded and blinded. Due to variability of clopidogrel results these tests are unreliable for determining patient treatment assignment.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists only from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the randomised study treatment. The EUCLID Study Physician should be consulted via the clinical hotline prior to the investigator breaking the blind. The investigator will document and report the action, without revealing the treatment given to patient, to Duke Clinical Research Institute (DCRI) or AstraZeneca staff. The number of individuals at the study centre who become aware of the treatment status should be kept to the absolute minimum including keeping the patient blinded if possible. Treatment with study medication should be continued if considered appropriate.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study medication and that potentially require expedited reporting to regulatory authorities. Treatment code information will not be provided to the clinical team or the investigators of the study. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of study medication(s)

Table 2 Identity of study medication

Study Medication	Dosage form and strength	Manufacturer
Ticagrelor 90 mg	Plain, round, yellow, film-coated tablet, 90 mg	AstraZeneca
Ticagrelor placebo	Plain, round, yellow, film-coated tablet, containing zero active therapy (identical in appearance to active)	AstraZeneca
Clopidogrel 75 mg	Plain, round, pink, biconvex, film-coated tablet, 75mg	Sanofi-Aventis
Clopidogrel placebo	Plain, round, pink, biconvex, film-coated tablet, containing zero active therapy (identical in appearance to active)	Sanofi-Aventis

5.5.2 Doses and treatment regimens

At Visit 2 (Randomisation), eligible patients will be randomly assigned to 1 of 2 treatment groups: ticagrelor 90 mg twice daily, or clopidogrel 75 mg once daily. The two medications to be administered in the study have different appearances. Due to this and the different dosing schedules, all patients will need to take ticagrelor/placebo (round yellow tablets) twice daily and the clopidogrel/placebo (round pink tablets) once daily in a double-dummy fashion to guarantee the blinding:

1. ticagrelor 90 mg and clopidogrel placebo in the morning, ticagrelor 90 mg in the evening

OR

2. ticagrelor placebo and clopidogrel 75 mg in the morning, ticagrelor placebo in the evening

Randomisation and treatment pack assignment will be managed via the IVRS/IWRS and the first dose of study medication should be taken at Visit 2 before the patient leaves the centre. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hour intervals, for the remainder of the treatment period.

Study medication should be swallowed whole with water. Study medication can be taken with or without food. Study medication should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

Duration of treatment

All patients will be followed for an anticipated minimum of 25 months and up to approximately 40 months. However, the actual duration of the study will be based on accrual of the predetermined number of events (1364) for the primary endpoint, and therefore the study may be shorter or longer than 40 months. The expected median duration is 32 months. A study closure plan will be developed that accounts for the patient recruitment pattern and the event rate to reach the predetermined number of primary events (target: 1364). It is intended that all randomised patients, including patients who discontinue from treatment or study prematurely, will undergo an ESTV or PTDV and an SCV as described in Table 1.

As safety is continuously monitored, the study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the DMC review. It is recommended that patients who have discontinued from treatment and are being followed by telephone (or agreed to be contacted at study closure) attend the final visit of the study in person.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

5.5.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The study medication label on the study supplies and the IB specifies the appropriate storage.

5.6 Concomitant and post-randomisation treatment(s)

Recording of concomitant medications will be made at each visit. Medications of special interest including study medication, other antiplatelet medications, proton-pump inhibitors (PPIs) and statins will be captured in detail. Other medications of interest will be captured by class and ongoing use. Complete concomitant medication information will be recorded peri-event for any SAE or permanent discontinuation of study medication due to an AE.

5.6.1 Oral antiplatelet therapies

Concomitant ASA at start of study: Patients requiring dual antiplatelet therapy (e.g. aspirin plus clopidogrel, aspirin plus prasugrel, or aspirin plus dipyridamole) will be excluded at study entry, as the purpose of this study is to primarily test the benefits of mono-antiplatelet therapy.

- **Low Dose ASA (defined as ≤ 150 mg od) added during the study:** patients who develop an indication for aspirin therapy after randomisation will follow the guidelines below. If concomitant ASA is needed during the study, it will be sourced locally.

  If the patient develops ACS (per AHA/ESC definition) or undergoes Percutaneous Coronary Intervention (PCI) without having ACS:

  - The patient should receive a loading dose of ASA (determined and recorded by the treating investigator) and then daily low-dose ASA thereafter (defined as ≤ 150 mg od) consistent with current practice guidelines.

  - The patient should continue to take study medication.

  - If a loading dose of ticagrelor or clopidogrel is desired, the investigator should utilise the study medications, giving both of the double-dummy medications, eg, to load for an interventional procedure (PCI), take (1) additional ticagrelor/placebo tablet and (4 to 8) additional clopidogrel/placebo tablets; the investigator will determine how many (4 to 8) of the clopidogrel tablets to be taken depending on the desire to load with 300mg or 600 mg of clopidogrel.

  If the patient requires peripheral percutaneous revascularization:

  - Following Bare Metal Stent implantation, concomitant low dose ASA (defined as ≤ 150 mg od) is recommended for up to 1 month duration per current guidelines.

- Following Drug Eluting Stent implantation, concomitant low dose ASA (defined as ≤ 150 mg od) is recommended for a minimum of 1 month duration per current guidelines.

If the patient suffers a stroke:

- The patient will stop study medication immediately following the stroke event.

- The investigator will treat the patient according to current practice guidelines. Once it is considered safe and the investigator is willing, the patient will resume blinded monotherapy study medication.

- **Use of High Dose ASA (> 150 mg)**

  The concomitant use of aspirin in any dose > 150 mg during the study is permitted only as a single, loading dose, regardless of circumstances (ie, prior MI, ACS, stroke, stent placement of any kind, etc). Long-term maintenance doses of aspirin > 150 mg are not permitted.

Other ADP receptor blockers (eg, prasugrel, ticlopidine):

Planned concomitant treatment with any of other ADP receptor blockers is not allowed in the study. If open-label treatment with any of these drugs is considered essential during the study, blinded study medication must be discontinued but may be resumed when open-label treatment with the ADP receptor blocker drug is stopped.

Dipyridamole

Planned concomitant chronic treatment with dipyridamole is not allowed in the study. If open-label treatment with dipyridamole, whether or not in combination with aspirin, is considered essential during the study, blinded study medication must be discontinued but should be resumed when open-label treatment with dipyridamole is stopped.

5.6.2 Approved PDE3 inhibitors for claudication (eg, cilostazol)

Planned concomitant treatment with any approved PDE3 inhibitor (ie, cilostazol) is permitted during the study.

5.6.3 Non-steroidal anti-inflammatory drugs (NSAIDs)

Clinical experience with NSAIDS in combination with ticagrelor is limited at this time. Treatment with NSAIDS is allowed during the study at the investigator's discretion. However, chronic daily dosing with non-selective NSAIDS (eg, patients with rheumatoid arthritis) may increase the potential for gastrointestinal bleeding, so either alternative therapy or concomitant acid suppression therapy is recommended. Treatment with selective cycloxygenase-2 inhibitors is permitted, although use is cautioned (Antman 2007). When pain management is needed, acetaminophen is preferred. Chronic therapy with aspirin for pain is prohibited.

5.6.4 Parenteral anticoagulants

Short-term treatment (ie, up to 7 days) with approved parenteral anticoagulants (eg. unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, fondaparinux) is allowed. However, long-term treatment with LMWH or fondaparinux in outpatients (at venous thrombosis treatment or atrial fibrillation doses) in combination with study medication is not allowed. Concomitant treatment with venous thrombosis prophylaxis doses is allowed. If long-term treatment with parenteral anticoagulant drugs at therapeutic doses is considered essential during the study, study medication must be discontinued, but should be resumed if parenteral anticoagulant therapy is stopped.

5.6.5 GPIIb/IIIa receptor antagonists

Short-term treatment (ie, up to 7 days) with GPIIb/IIIa receptor antagonists is allowed during the study.

5.6.6 Oral anticoagulants

Concomitant treatment with oral anticoagulant drugs (ie, vitamin K antagonists, direct thrombin inhibitors, factor X inhibitors) is not permitted during the study. If treatment with oral anticoagulant drugs is considered essential during the study, study medication must be discontinued, but should be resumed if oral anticoagulant therapy is stopped. Patients should continue to be followed as defined in section 5.8.1.

5.6.7 Fibrinolytics

Clinical experience with fibrinolytics in combination with ticagrelor is limited at this time and caution should be used. If a patient is to be treated with fibrinolytic therapy, study medication should be stopped and restarted no earlier than 24 hours after completion of fibrinolytic therapy and when the risk of bleeding is deemed low in the judgment of the investigator.

5.6.8 Digoxin and other p-glycoprotein interactions

Ticagrelor modestly increases digoxin levels. Therefore digoxin levels should be monitored closely following initiation of study medication and with any change in study medication. Other p-glycoprotein substrates may be expected to have similar changes in pharmacokinetics. For additional details reference the IB.

5.6.9 CYP450 interactions

5.6.9.1 CYP3A inhibitors

Strong inhibitors of CYP3A enzyme (eg, ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin [but not erythromycin or azithromycin], nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, or over 1 litre daily of grapefruit juice) should not be co-administered with ticagrelor, as plasma levels of ticagrelor would be substantially increased.

5.6.9.2 CYP3A substrates or inducers

Concomitant therapy with simvastatin or lovastatin at doses higher than 40 mg daily is not permitted since administration with ticagrelor will result in higher serum concentrations and may put patients receiving more than 40 mg per day of simvastatin or lovastatin at increased risk of statin-related adverse effects. There are no restrictions to other statin therapies (ie, doses of simvastatin or lovastatin ≤ 40 mg daily or any dose of any other statin is permitted). Investigators are advised to check lipid levels and adjust statin dosages per local practice and appropriate guidelines.Standard monitoring of patients for possible statin-associated myopathy should be conducted.

Co-administration of ticagrelor with strong inducers of CYP3A also should be avoided (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital).

Discontinuation of study medication is up to the judgment of the investigator. If continued antiplatelet medication is judged necessary, there may be a need for extra caution regarding bleeding tendency.

5.6.9.3 CYP2C19 inhibitors

Ticagrelor is not metabolised via CYP2C19. In contrast, clopidogrel is a prodrug that needs to be metabolised to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Thus, for patients who are being treated with study medication (ie, potentially randomised to clopidogrel treatment), the use of omeprazole or esomeprazole is prohibited, however the use of other proton pump inhibitors (PPIs) is allowed. Avoid concomitant use of other strong or moderate CYP2C19 inhibitors during the study. The concomitant use of PPIs will be recorded in the electronic case report form (eCRF).

5.6.10 Surgery

It is recommended that cardiac surgery and major non-cardiac surgery that in the opinion of the Investigator poses a risk for clinically major bleeding not be performed until at least 5 days after stopping study medication to avoid excessive bleeding. However, one should follow local treatment guidelines and protocols. There is a trade-off between stopping study medication too early and risking thrombotic events versus continuing treatment too close to surgery and risking haemorrhage. Thus it is also recommended that study medication not be discontinued for significantly longer than 5 days so as to minimise the risk of thrombotic complications while off study medication.

Other medication, which is considered necessary for the patient’s safety and well being, may be given at the discretion of the investigator.

After surgery, study medications should be restarted when the risk of bleeding is deemed low in the judgment of the investigator.

5.6.11 Other surgery and invasive non-cardiovascular procedures

For other surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator. As with all other surgeries, investigators should collect and record all peri-procedural bleeding events.

After the surgery or procedure, study medications should be restarted (if interrupted) as soon as possible. Regarding prevention of postoperative thrombosis, see Section 5.6.4.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator.

5.7 Treatment compliance

The administration of all medication (including study medications) should be documented in the patient's medical record and recorded in the eCRF where appropriate.

Patients will be asked to return all unused study medications and empty packages to the clinic at each visit. The patient's compliance will be assessed by the investigator or designee and recorded in the eCRF. A pill count should be done at a patient level and recorded in the eCRF and a dispensing log by the study centre personnel.

5.7.1 Accountability

The study medication provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study medication dispensed and returned. This record keeping consists of a dispensing log including the identification of the person to whom the drug is dispensed, the quantity dispensed, the date of dispensing, the quantity returned and the date returned.

Patients will be asked to return all unused study medication to the investigational centre at each visit. The investigator or delegate will enter the amount of returned tablets on the eCRF and make an assessment regarding patient treatment compliance. In addition, the investigator or delegate will enter the amount of returned tablets on the dispensing log or similar log according to local practice at centre. Any patient found to be noncompliant will be counselled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator will retain the returned medication until the study monitor or delegate collects it, along with any medication not dispensed. The monitor is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is returned to the sponsor and/or destroyed. Following drug accountability, the study monitor or delegate will advise on the appropriate

method for destruction of unused study medication. Destruction of study medication must only be conducted by an authorised centre.

5.8 Discontinuation of study medication

Patients should be discontinued from study medication in the following situations:

5.8.1 Temporary discontinuation from study medication

- Severe thrombocytopenia (platelet count < 50,000/uL). Patients may restart study medication once the severe thrombocytopenia resolves and if considered appropriate by the investigator.
- Surgery or procedures associated with major haemorrhage, see Section 5.6.10
- Major bleeding, see Section 6.4.5.2
- Need of treatment with prohibited concomitant medications, see Section 5.6
- Stroke, see Section 5.6.1

For other surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator, see Section 5.6.10.

5.8.2 Permanent discontinuation from study medication

- Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Investigator's decision:

1 Incorrectly enrolled patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk

2 Adverse Event for which the Investigator thinks continued treatment may put the patient at undue risk

3 Severe non-compliance to study protocol

4 Pregnancy

Discontinuation of study medication does not mean discontinuation of follow-up or termination of study participation. Each permanent discontinuation should be communicated to the study team. For decisions around permanent discontinuation the EUCLID Study Physician can be consulted through the clinical hotline. Study assessments or telephone follow-up should be continued in all cases if possible, see Sections 5.8.3 and 5.9.

5.8.3 Procedures for discontinuation of a patient from study medication

Patients permanently discontinuing study medication should be given conventional therapy, if applicable, and should always be asked to continue the regular visits as described below.

A patient that decides to discontinue study medication will always be asked about the reason(s) for their desire to discontinue study medication and the presence of (if any) adverse events. These data will be ascertained and documented by the Investigator and recorded in the eCRF as appropriate. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); and the patient should return all study medications.

It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. Complete withdrawal from the study (withdrawal of consent) has a direct impact on the potential validity of all study data and should be avoided wherever possible.

If the patient permanently discontinues study medication prior to the closure of the study, there could be several different options for their continuation in the study as described below.

5.8.3.1 The patient agrees to undergo the premature treatment discontinuation visit and then continue in-person study visits

The patient agrees to undergo the Premature Treatment Discontinuation Visit (PTDV) and then continue in-person study visits according to plan. This is the preferred option and patients who discontinue study medication will always be asked if they agree to this approach. If agreed, as above, the patient will undergo their PTDV at the time study medication is stopped. The patient will continue attending subsequent study visits according to schedule (Table 1) until the end of study date (ie, PACD) is declared, ie, when the pre-specified number of primary events has been reached. The patient will then return for their Study Closure Visit (SCV) as soon as possible but not later than 60 days after the Primary Analysis Censoring Date (PACD) has been declared. It is essential that whenever possible all patients attend the SCV in person.

5.8.3.2 The patient unwilling to continue in-person study visits but agrees to undergo modified follow-up

If the patient agrees, the PTDV visit should be done. The subsequent visits until the end of study date will be done as modified follow-ups (eg, regular telephone contacts, a contact at study closure, or other means) as specified in Section 5.8.3 in order to ascertain whether any endpoints or safety events had occurred. Such a patient has not withdrawn his/her consent or withdrawn from the study.

5.8.3.3 The patient refuses any form of follow-up

If the patient refuses any form of follow-up, he/she officially withdraws from the study and withdraws consent. This approach should be avoided if possible and is further described in Section 5.9. This decision must be documented (see Section 5.9). At the end of the study, vital status on all such patients will be collected by checking medical records or from publicly available sources, in accordance with local regulations.

5.8.4 End of Study Treatment Visit

At the End of Study Treatment Visit (ESTV) physicians caring for the patient will decide which locally available antiplatelet medication the patient should receive as part of his/her ongoing clinical care. This medication(s) will be open label and obtained locally.

5.9 Withdrawal from study (study medication and assessments)

Patients are at any time free to withdraw from the study (ie, discontinue study medication permanently and withdraw from visit assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF). The ICF should be re-signed and dated by both the patient and the investigator, if possible. Such patients will always be asked about the reason(s) and the presence of any adverse events. The reason for permanent discontinuation of treatment with the study medication and the date of the last intake of the study medication must be documented in the eCRF.

Patients permanently discontinuing from study medication should be given conventional therapy, if applicable, and should always be asked to continue to attend protocol visits as described in Section 5.8.3. If the patient denies any additional protocol follow-up and officially withdraws consent from the study one of the alternatives a) to c) should be followed:

(a) At the time of discontinuation of treatment and withdrawal of consent from continued assessment the patient should, if possible, undergo the PTDV. The patient should return all study medication.

(b) If the patient does not agree to this option (which must be documented), a modified PTDV (eg, a telephone contact) should be arranged. The approach taken should be documented. The patient should return all study medication.

(c) If the patient does not agree to a) or b) this must be documented in the patient's medical record. The patient should return all study medication.

At the end of the study, vital status will be collected for all patients who withdraw consent by checking medical records or by collecting information from publicly available sources, in accordance with what local regulations allow when informed consent has been withdrawn.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at the Study Closure Visit. AstraZeneca or delegate will therefore attempt to collect information on **all** patients' vital status from publicly available sources at the Study Closure Visit, even if informed consent has been withdrawn completely.

Withdrawn patients will not be replaced.

5.10 Study committees

5.10.1 Committee organization

In consideration of the large nature of this study, several key groups will act as alliances to provide direction and guidance throughout this study. The Executive Committee is responsible for the study design, study oversight and reporting of the results. The Executive Committee will serve as the Publications Committee. The International Steering Committee will provide regional oversight, focus on enrolment milestones and selected expertise, whereas the Operations Committee involves study tactics and is operational in nature.

All committee meetings, unless otherwise noted, are considered open in that others may join in a listening-only mode, but only if invited by the committee Chair.

5.10.1.1 Executive committee

The Executive Committee will be responsible for the overall study design, conduct, analysis and interpretation, supervision and reporting of the study results, including the development of the protocol, any protocol amendments and the publication Statistical Analysis Plan. The Executive Committee, together with the sponsor, will decide whether or not to stop the study based on the information from the DMC. The Executive Committee membership will be comprised of designated international academic leaders and members of the Sponsor, and will operate under a separate Charter. The Executive Committee will also serve as the Publications Committee.

5.10.1.2 International steering committee

The International Steering Committee will be selected and supervised by the Executive Committee and will be responsible for providing clinical guidance on study implementation and conduct of the study. The International Steering Committee will comprise all the national lead investigators and other selected principal investigators and all members of the Executive Committee.

5.10.1.3 Operations committee

The Operations Committee will be comprised of Study Physicians and Project Managers from DCRI and AstraZeneca. The Operations Committee will be responsible for harmonizing global delivery of the study within the operations model.

5.10.2 Independent data monitoring committees

Two independent data monitoring committees will be appointed. A Clinical Event adjudication Committee (CEC) will adjudicate primary and secondary endpoints (see Section 12.4.1) and an independent Data Monitoring Committee (DMC) will be responsible for assessing safety during the study (see Section 12.4.2).

6. COLLECTION OF STUDY VARIABLES

The investigator will ensure that data are recorded in a timely fashion on the eCRF as specified in the study protocol and in accordance with the instructions provided.

6.1 Recording of data

The site investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). Data will be entered in the eCRF using a Web Based Data Capture (WBDC) system at the study centre. Study personnel will be trained and responsible for entering data specified in the protocol into the WBDC system and according to the eCRF Instructions. When data have been entered reviewed, edited, and Source Data Verification (SDV) performed as appropriate by AstraZeneca representative or delegate, the data will be frozen to prevent further editing. The site principal investigator will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study centre.

6.2 Data collection at enrolment and during the study

6.2.1 Enrolment procedures

Each patient will undergo enrolment procedures during Visits 1 and 2. The following data will be collected in the eCRF:

- Demographics (including sex, date of birth, race, ethnic group)
- Relevant medical and surgical history
- Urine pregnancy test (for females of child bearing potential)
- Laboratory samples for baseline chemistry, haematology and CYP2C19 polymorphism
- Current concomitant medications of interest
- Targeted physical examination including assessment of the following: lungs, cardiovascular, neurological evaluations
- Vital Signs
- ABI/TBI obtained using a Doppler ultrasonic instrument
- 12-lead electrocardiogram (ECG), heart rate and blood pressure
- EQ-5D questionnaire (baseline for patients' health related quality of life, will be collected at all clinics in countries where a validated form is available in the local language.)
- Peripheral Artery questionnaire (PAQ)

- Health resource utilization data including hospitalisation and long term care information

6.2.2 Protocol procedures during the study

Patients will have routine visits and procedures as outlined in Section 3.1. Any new suspected endpoint events, non-serious AEs of interest, DAEs, SAEs and current medications will be recorded in the eCRF as described in Section 5.6. It will be the responsibility of the Investigator to obtain all necessary source documents, including medical records from institutions where a hospitalisation may have occurred.

If the patient experiences a suspected clinical efficacy endpoint event or a bleeding event, the following actions should be taken whenever possible and in accordance with current guidelines and local practice standards (refer to Appendix E Endpoint Definitions for further details):

Symptoms of cardiac ischaemia (ie, potentially representing unstable angina or MI):

- Cardiac biomarkers of necrosis (troponin and/or creatinine kinase myocardial band [CK-MB]) should be collected serially and measured by local labs according to local standards for at least 24 hours. The sites are encouraged to use recent guidelines.
    - According to the ESC/ACCF/AHA/WHF Expert Consensus Document, blood samples for the measurement of troponin should be drawn on first assessment (often some hours after the onset of symptoms) and 6–9 h later (ESC/ACCF/AHA/WHF 2007). Occasionally, a patient may require an additional sample between 12 and 24 h if the earlier measurements were not elevated and the clinical suspicion of myocardial infarction is high. To establish the diagnosis of myocardial infarction, one elevated value above the decision level is required. If troponin assays are not available, the best alternative is CKMB (measured by mass assay). As with troponin, an increased CKMB value is defined as a measurement above the 99th percentile URL, which is designated as the decision level for the diagnosis of myocardial infarction. Gender-specific values, if relevant, should be employed. The CKMB measurements should be recorded at the time of the first assessment of the patient and 6–9 h later in order to demonstrate the rise and/or fall exceeding the 99th percentile URL for the diagnosis of myocardial infarction. An occasional patient may require an additional diagnostic sample between 12 and 24 h if the earlier CKMB measurements were not elevated and the clinical suspicion of myocardial infarction is high.
- A standard 12-lead ECG should be obtained during or as soon after the episode of ischaemia as possible and serially according to local standards until resolution of symptoms.

Coronary Revascularisation (ie, PCI or CABG):

- Cardiac biomarkers of necrosis (troponin and/or CK-MB) should be measured locally immediately before the procedure and serially (every 8 hours x3 or until hospital discharge) after the procedure.
    - According to the ESC/ACCF/AHA/WHF Expert Consensus Document, the occurrence of procedure-related cell necrosis can be detected by measurement of cardiac biomarkers before or immediately after the procedure, and again at 6–12 and 18–24 h **(**ESC/ACCF/AHA/WHF 2007**)**.Elevations of biomarkers above the 99th percentile URL after PCI, assuming a normal baseline troponin value, are indicative of post-procedural myocardial necrosis. If cardiac troponin is elevated before the procedure and not stable for at least two samples 6 h apart, there are insufficient data to recommend biomarker criteria for the diagnosis of peri-procedural myocardial infarction

- A standard 12-lead ECG should be obtained before the procedure, immediately post-procedure, and, if possible, in the morning following the procedure.

- For patients undergoing major surgery, all banked blood products administered (ie, the number of packed red blood cell or whole blood transfusions, fresh frozen plasma, platelets [volume in mL] and cryoprecipitate) and those undergoing CABG, the chest tube output in the first 24 hours should be noted.

Focal neurological symptoms (ie, potentially representing stroke or transient ischaemic attack):

- Complete neurological exam.

- Brain imaging (computerized axial tomography [CT] or magnetic resonance imaging [MRI]).

Bleeding (either unexpected or of unanticipated quantity):

- Record last stable haemoglobin before start of bleeding (or hematocrit if haemoglobin unavailable). Haemoglobin (or hematocrit if haemoglobin unavailable) should be measured locally serially until resolution of the bleeding.

- Record the date, time and number or volume of all banked blood products administered.

Patient health-related quality of life:

- EQ-5D questionnaire as described in Section 6.5.1

- PAQ as described in Section 6.5.2

Health care resource utilisation:

- Information on hospitalisations as described in Section 6.9
- Information on rehabilitation as described in Section 6.9
- Information on long-term care as described in Section 6.9

6.3 Efficacy

Suspected clinical efficacy endpoints will be collected in the eCRF. These events will be identified using standard questioning of the patient at each visit, or by information that the investigator may receive as part of standard medical practice. Safety endpoint events will be identified similarly.

For each suspected endpoint, the investigator will complete information specific to that type of endpoint on the eCRF and compile relevant additional source information where required. Once all relevant information has been collected from the centre, the endpoint will be sent to the CEC for central adjudication. It is essential that investigators collect all relevant and required end point data as soon as possible. Investigators must report all suspected endpoints in the eCRF, even those that may not meet strict definition, to ensure all potential endpoints are reviewed and adjudicated by the CEC. Please refer to Appendix E for details regarding the endpoint definitions.

6.3.1 Death

All deaths reported post-randomisation will be recorded and adjudicated.

6.4 Safety

The site Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. See section 6.4.4.1 for details on reporting of SAEs that are also endpoints in the study.

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Only non-serious AEs of interest (ie, bleeding events, dyspnoea, renal impairment/increased creatinine, bradyarrhythmia, increased LFTs, gout/uric acid increases, pneumonia, gynecomastia, abnormal uterine bleeding and all malignancies excluding non-melanoma skin cancers) and DAEs will be collected from time of randomisation throughout the treatment period and including the follow-up period, until the Study Closure Visit.

All SAEs will be recorded from the time of informed consent, with the exception of events defined as disease progression (see Section 6.4.3.1) and those described in Section 6.4.4.1.

SAEs will be recorded at all visits in patients who prematurely discontinue treatment with study medication. Non-serious AEs of interest and DAEs will be recorded until the Study Closure Visit but no less than 30 days after last dose of study medication.

Follow-up of unresolved adverse events

Any non-serious AEs of interest, DAEs and SAEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s) of interest /SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected and recorded for each **non-serious AE of interest and DAE:**

- AE
- the date when the AE started and stopped
- investigator causality rating against the Study Medication (yes or no)
- action taken with regard to study medication
- outcome

In addition, the following variables will be collected and recorded for **SAEs:**

- SAE (verbatim)
- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed (if performed)
- Autopsy results
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE
- Date and time of last dose of study medication before AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not a SAE. On the other hand, low grade cancer with an excellent prognosis may be considered "mild" in severity, but would still be reported as an SAE.

The following definitions for intensity rating are:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

Causality collection

The Investigator will assess causal relationship between Study Medication and each AE, and answer "yes" or "no" to the question, "Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?"

Causal relationship in cases where the relationship is ascribed to disease progression will be classified as no reasonable possibility.

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse Events based on signs and symptoms

The patient will spontaneously report all AEs and SAEs in response to the open question from the study personnel: *"Have you had any health problems since the previous visit/you were last asked?"* The study personnel will only record non-serious AEs of interest, DAEs and SAEs that were reported by the patient or revealed by observation in the eCRF. When collecting DAEs and SAEs, the recording of diagnoses (when possible) is preferred to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Baseline (Visit 1) laboratory variables will be analyzed at local laboratories for all patients as specified in Section 6.4.6. Follow-up testing for abnormal laboratory results should be performed according to local practice.

After Visit 1, laboratory safety assessments will not be routinely done, but may be performed locally at the investigators discretion. Relevant lab values will be captured in the eCRF. In association with a suspected endpoint event, different assessments may have to be undertaken

which could include local laboratory assessments and will be recorded in the eCRF as appropriate.

The results from protocol-mandated laboratory assessments and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in investigator-initiated assessment of laboratory values and protocol-mandated vital signs should therefore only be reported if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study medication.

If a non-serious AE of interest or SAE is detected through deterioration in a laboratory value/vital sign and is associated with clinical signs and symptoms, the sign or symptom will be reported and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, renal failure versus increasing creatinine). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as for non-serious AEs of interest and SAEs.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

NB. Cases where a patient shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥ 3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D for 'Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law'.

6.4.3.1 Disease progression

Disease progression can be considered as a worsening of a patient's clinical condition attributable to the disease in the patient population for which the study medication is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of the following cardiovascular and peripheral artery disease events will be recorded in the eCRF, however they should be considered as disease progression and will not be reported as an AE/SAE during the study.

- Severe recurrent cardiac ischaemia or recurrent cardiac ischaemia
- Unstable Angina
- Hospitalisation for PCI or CABG
- Transient ischaemic attack
- Hospitalisation for major amputation due to PAD or limb revascularization
- Hospitalisation for claudication, ischaemic ulcer or rest pain including debridement, antibiotic treatment or hydration for imaging
- Development of a lower extremity necrotic wound or increasing size of existing necrotic wound

- Lower extremity gangrene
- Major amputation due to PAD
- Progression of Rutherford stage of symptoms

6.4.4 Reporting of serious adverse events

All SAEs as defined above have to be reported, whether or not they are considered causally related to the study medication, or to the study procedure(s).

If an SAE meeting the reporting criteria occurs during the course of the study, the investigators or centre personnel must inform appropriate DCRI representatives by reporting the SAE, within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigator or centre personnel report an SAE in the eCRF, an automated email alert is sent to the DCRI Safety Surveillance representative.

The designated DCRI representative works with the investigator to ensure that all the necessary information is recorded in the SAE module of the eCRF as appropriate. The SAE data is then reported to the AstraZeneca Patient Safety data entry centre **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other centre personnel inform DCRI representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

If the eCRF system is not available, a back-up paper based process will be implemented for SAE reporting. The Investigator or study centre personnel will use this system to report an SAE to the appropriate DCRI Safety Surveillance representative via fax. Once the eCRF becomes available the Investigator or study centre personnel will record the SAE data within the eCRF module as appropriate.

The DCRI representative will then advise the Investigator/study centre personnel how to proceed.

6.4.4.1 Reporting of serious adverse events that are also endpoints in the study

The following endpoints in the study, although qualifying as SAEs will be reported only as endpoints and these will be followed by the independent DMC:

- Non-fatal MI
- Ischaemic Stroke

- CV Death

These endpoints will not be reported to health authorities as SAEs to avoid unnecessary unblinding of efficacy endpoints that are also SAEs. All other events when meeting SAE criteria will be reported as SAEs, with the exception of procedural related bleeding if expected for the procedure and those events due to CV or PAD progression as defined in Section 6.4.3.1.

If it is determined by the CEC that suspected endpoint events do not meet endpoint criteria or disease progression per Section 6.4.3.1 and serious criteria are met, the events will be captured as SAEs and reported to health authorities as appropriate.

6.4.5 Bleeding events

For all bleeding events, the investigator will complete information on the eCRF specific to that bleeding event. In addition, for all reported bleeding events (excluding those which are self-limited and do not prompt medical evaluation or intervention) relevant information will be compiled and sent to the CEC for central adjudication. Additionally, bleeding events will be reported as AE of interest and SAEs if serious criteria are met.

The CEC will adjudicate and evaluate bleeding events (excluding minimal) according to the following bleeding definitions: TIMI and PLATO. BARC and ISTH bleeding profiles will be captured for each patient where appropriate but will not be formally adjudicated (Mehran 2011, Schulman 2005).

6.4.5.1 Bleeding associated with procedures

Bleeding associated with procedures should be reported as an AE/SAE if exceeding normal bleeding for the specific procedure.

6.4.5.2 Procedures for study medication in case of bleeding

Study medication must be stopped immediately in case of a bleed deemed to be clinically significant in the judgment of the investigator (eg, a significant fall in haemoglobin, need for transfusion, haemodynamically significant, or in a critical location such as intracranial, intraspinal, intraocular, or pericardial), but may be reinstated when the risk of bleeding is deemed low in the judgment of the Investigator and if not contraindicated. The study medication administration need not be stopped in case of a minor bleeding. All bleedings should be treated and followed up according to local clinical practice. Major bleeding events should be managed according to need with general support and blood. It should be noted that platelet transfusion may or may not reverse bleeding in a patient receiving ticagrelor as the new platelets may be inhibited by ticagrelor as long as it is circulating in the blood. For this reason, investigators should not unblind in order to decide whether or not to treat or withhold platelet transfusions.

There is currently no antidote to ticagrelor and treatment of bleedings should therefore be symptomatic and handled according to the clinical routines at the investigational centre.

6.4.6 Laboratory safety assessment

The following laboratory variables will be analyzed at local laboratories for all patients, at baseline (Visit 1) and at ESTV or PTDV:

Clinical chemistry (S denotes serum)	Haematology (B denotes whole blood)
S-Creatinine	B-Haemoglobin
S-Alkaline phosphatase	B-Haematocrit
S-Aspartate aminotransferase (AST)	B-Platelets and MPV
S-Alanine aminotransferase (ALT)	B-White blood cells
S-Total Bilirubin (Elevated values to be fractionated)	B-White blood cells (with differential if abnormal)
S – Albumin	B-Haemoglobin A1c (only diabetics)
S-glucose	
S-Total, LDLc, HDL cholesterol	

Other

- CYP2C19 polymorphism sample (collected only at enrolment visit and analyzed at a central lab).
- Proteinuria and hematuria measured with urine dipstick.
- A urine pregnancy test will be performed at the investigational centre at Visit 1 for all females of child-bearing potential.

At the follow-up visits, laboratory safety assessments will not be routinely done, but may be performed locally at the investigators discretion. In association with a suspected endpoint event, different assessments may have to be undertaken which could include local laboratory assessments. Follow-up testing for abnormal laboratory results should be performed according to local practice.

See Section 6.4.3 for AEs based on examinations and tests.

For blood volume see Section 7.1.

6.4.6.1 Management of abnormal liver chemistry tests

The investigator should report any patient meeting potential Hy's Law criteria; AST or ALT ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2x ULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe. Potential cases should be reported for patients on or off study treatment from Visit 1 through the Closure Visit to the appropriate AstraZeneca representative.

In case a patient shows an AST **or** ALT ≥ 3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law'.

6.4.7 Physical examination

A targeted physical examination will be performed at Visit 2 by medically qualified individuals and include an assessment of the following: lungs, cardiovascular, abdominal, neurological evaluations, height, weight, and ABI. Results will be recorded as an overall normal or abnormal with a listing of abnormalities.

6.4.8 ECG

An ECG should be performed according to local clinical practice to document any occurrences of MI or recurrent cardiac ischaemia during the study, see 6.2.2 for further details.

6.4.8.1 Resting 12-lead ECG

Standard 12-lead ECGs will be recorded and assessed locally at Visit 2.

ECGs should be standard 12-lead ECG with a lead II rhythm strip, covering at least 5 complexes in the supine position after the patient has rested in this position for 5 minutes.

6.4.9 Vital signs

Heart rate, systolic blood pressure (BP) and diastolic BP will be assessed using non-invasive equipment after the patient has been at rest for 5 minutes.

6.5 Patient reported outcomes (PRO)

Patients' health related quality of life will be measured using the EQ-5D quality of life questionnaire and the Peripheral Artery Questionnaire (PAQ).

6.5.1 European quality of life-5 dimensions questionnaire

The EQ-5D has been extensively used within the cardiovascular field to assess patient health related quality of life in studies of new treatments and has showed both high validity and reliability (Dyer 2010).

The EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ-Visual Analogue Scale (EQ-VAS). The EQ-5D descriptive system is a self-administered instrument consisting of five questions, each representing one dimension (Brooks 1996). The five dimensions are mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. For each dimension responders are asked to state their status on a three level ordinal scale; whether they experience no problems (level 1), some problems (level 2) or severe problems (level 3). Health states defined by the 5 dimensions can be converted into a weighted health state index (health state utility) by applying scores from the EQ-5D value sets elicited from general population samples (Dolan 1997). The EQ-VAS records the respondent's self-rated health on

a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

The EQ-5D paper form will be filled in by the patients under the supervision of the study staff. The study staff will transfer the responses into the eCRF. All patients will be asked to complete the EQ-5D questionnaire at Visit 2 then annually starting at the 12-month visit and at the PTDV or ESTV. The EQ-5D will only be administered in countries where an official language version is available. Descriptive analysis and reporting of the data will be carried out in the CSR including converting the EQ-5D to utilities using the United Kingdom tariff for all patients. Additional analysis using the single index value to support cost-effectiveness analysis will be reported separate from the main study in a separate health economic (HECON) sub-study report.

6.5.2 Peripheral artery questionnaire

The PAQ instrument has been demonstrated to be a valid, reliable and responsive disease specific instrument for patients with PAD (Spertus 2004). The PAQ instrument will be administered at all clinics in countries where a validated form is available in local language.

Patients will be asked to complete the PAQ at Visit 2 then annually starting at the 12-month visit and at the PTDV or ESTV. Descriptive analysis of patients' health related quality of life using the PAQ instrument will be reported in the CSR.

6.6 Pharmacokinetics (not applicable)

6.7 Pharmacodynamics (not applicable)

6.8 Pharmacogenetics (not applicable)

6.9 Health economics

Information on health care resource utilization associated with hospitalisations admissions, rehabilitation, long-term care and health related quality of life (EQ-5D) will be collected to enable health technology assessment, health economic analysis and health economic modelling. Resource utilization and health related quality of life will be recorded in the eCRF with start at randomisation. The following types of resources will be recorded for all hospitalisations, rehabilitation in hospital and long-term care:

- Admission date
- Discharge date
- Discharge destination

- Ward type information including duration of stay
    - General
    - Cardiology (potentially included in above)
    - Critical care unit (CCU)
    - Intensive care unit (ICU)
- Final discharge diagnosis
- Major secondary discharge diagnosis (if present)
- Main procedures
- UB-form billing information from the United States

The variables collected to support health economic evaluation are the EQ-5D questionnaire at randomisation (baseline), every 12 months thereafter and at the ESTV/PTDV as well as information on all hospitalisations, rehabilitations and on long-term care, during the course of the study will also be ascertained. Descriptive reporting of the resource utilization data and health related quality of life data based on the EQ-5D will be carried out in the CSR. The data will be combined with economic data and life expectancy data collected independently of the study to construct comparative health economic analyses between treatment groups. The economic analysis and cost-effectiveness analyses that include data external to the study will not be included in the CSR.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 3 below. The collection of additional samples is performed locally at the discretion of the investigator and recorded in the eCRF as appropriate.

Table 3 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
	Clinical chemistry	**5**	**2**	**10**
	Haematology	**3**	**2**	**6**
	CYP2C19 Polymorphism sample	**2**	**1**	**2**
Total				**18 mL**

7.2 Handling, storage and destruction of biological samples

The baseline and end of treatment laboratory samples (see Section 6.4.6) and any laboratory safety samples taken at the investigators discretion or connected to an endpoint event will be analysed locally. The safety samples will be used up or disposed of after analyses. The CYP2C19 polymorphism sample will be collected at the enrolment visit and analyzed at the central laboratory. All samples will be destroyed after CYP2C19 polymorphism sample analysis.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre will ensure full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study centres and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca

- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(s) holding the samples is/are informed about the withdrawal of sample consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study centre

- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study centre.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC)/ Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study centre staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca or its designee before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca or delegate should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or delegate will provide Regulatory Authorities, EC/IRB and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the ECs/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study medication per the EC/IRB requirements. AstraZeneca or delegate will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study including the importance of continued follow for endpoints and safety events event until the end of the study even if study medication has been discontinued

- Ensure each patient is notified that they are free to discontinue from study treatment and assessments at any time but should continue to be followed for endpoint and safety events

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Executive Committee and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca or delegate will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca (or delegate) and the centre's EC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including SDV. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca or its delegate immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it may be necessary for a representative of AstraZeneca or its delegate to visit the investigational study centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca or delegate and the investigator.

9.2 Training of study centre personnel

Before the first patient is entered into the study, an AstraZeneca representative or delegate will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and documented, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff) and document appropriate training per their study specific role/responsibility.

9.3 Monitoring of the study

During the study, an AstraZeneca or DCRI representative will have regular contacts with the study centre, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study medication accountability checks are being performed
- Perform source data verification (SDV) (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure any withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca or DCRI representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

Access to source documents and source data is essential to inspection and review of clinical studies and inspection of clinical study centres by the Food and Drug Administration (FDA).

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between DCRI or AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The study is expected to start in Q4 2012 and to be completed by Q1 2016.

The investigators will be notified when recruitment is complete.

The end of the entire study is defined as "the last visit of the last patient undergoing the study".

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. The Executive Committee may terminate enrolment in a country in order to ensure a reasonable international distribution of patients. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ticagrelor.

10. DATA MANAGEMENT

Data management will be performed by Duke Clinical Research Institute (DCRI).

The data collected through third party sources will be obtained and reconciled against study data.

The DCRI will be responsible for medical coding. Adverse events will be coded using DCRI's current version of the medical dictionary for regulatory activities (MedDRA) updated semi-annually. Medications will be classified according to the AstraZeneca drug dictionary that AstraZeneca will provide to DCRI.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable (not applicable)

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE) (not applicable)

11.3 Calculation or derivation of patient reported outcome variables

The EQ-5D data will be used to calculate utility weights based on the UK tariff. The EQ-5D data will be reported in the CSR. To the extent the EQ-5D data is used for health economic modeling this will be reported outside the CSR as part of subsequent health economic analyses. In addition, explorative analyses for differences in health related quality of life between the treatment groups will be performed. These analyses will also be reported separate from the CSR. Descriptive analyses of PAQ data will be reported in the CSR.

11.4 Calculation or derivation of pharmacokinetic variables (not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s) (not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (not applicable)

11.7 Calculation or derivation of health economic variables

All health care resource utilization data will be carried out as part of the CSR. The health care resource utilization data and the EQ-5D data will be used in combination with cost and life-table data to develop health economic analyses and cost-effectiveness analyses. These analyses will be carried by the HECON Sub-study Team and will be reported independently of the CSR.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Full analysis set (FAS)

All patients who have been randomised to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomised study medication irrespective of whether the event occurred before or following discontinuation of study medication. Patients who withdraw consent to participate in the study will be included up to the date of their study termination except for vital status known through public records (for use in the analysis of all-cause mortality). All efficacy variables will be analyzed using the FAS.

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomised ticagrelor or clopidogrel, and for whom post-dose data are available will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (eg, those randomised to ticagrelor but actually given clopidogrel) will be accounted for in the actual treatment group. If a patient received study drug from the wrong kit for only a part of the treatment duration and then switched to another, the associated actual treatment group for that patient will be the treatment group that patient was randomized to. Patients will be censored at 7 days after their last dose of study medication.

12.2 Methods of statistical analyses

12.2.1 Efficacy analysis

All efficacy analyses will be based on the intent-to-treat principle using the FAS, including only events adjudicated by the CEC. Investigators are instructed to report all suspected endpoints in the eCRF, even those that may not meet strict endpoint definitions, to ensure all potential events are reviewed and adjudicated by the CEC. The time from randomisation to the first occurrence of any event in the given endpoint will be compared using the Cox proportional hazards model with a factor for treatment group. The p-value, HR, and 95% confidence interval will be reported. No multiplicity adjustment will be made to the confidence intervals, as they will be interpreted descriptively and used as measures of precision. Kaplan-Meier estimates of the cumulative risk of each composite endpoint and its individual components will be calculated and plotted.

Primary efficacy variable:

The primary analysis will compare the time from randomisation to the first occurrence of any event in the composite endpoint CV death, MI and ischaemic stroke. Refer to Appendix E for definitions of CV death, MI and ischaemic stroke.

The null hypothesis will be that the risk/hazard of an event on ticagrelor is equal to the corresponding risk/hazard on clopidogrel:

H_0: HR (ticagrelor divided by clopidogrel) = 1

The alternative hypothesis will be that the HR is greater, or less than 1:

H_1: HR $\neq$ 1

The hypothesis will be tested at 4.94% two-sided significance level to account for the single planned interim analysis with the overall type I error preserved at 5%. If the DMC conducts additional interim analyses of the primary outcome, these levels will be adjusted accordingly using the alpha spending function. For definition of the significance level of the final analysis, see Section 12.2.3.

The HR and 95% confidence interval will be reported. Kaplan Meier estimates of the cumulative incidence to the first occurrence of any event in the composite endpoint will be calculated and plotted, as will the cumulative risk to the first occurrence of each component separately. The contribution of each component of the primary composite efficacy endpoint to the overall treatment effect will be examined.

The assumption of proportional hazards for the factor for treatment group will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses. An additional explorative analysis of the primary endpoint with cardiovascular death replaced by all-cause mortality will be performed.

To assess possible effects of informative censoring, sensitivity analyses will be done as follows. Based on the missing follow-up time in drop-outs, ie, the time from censoring to primary analysis censoring date, the expected number of events that might have been observed if all patients would have completed the study can be calculated using an event rate similar to that observed in the study. The comparison of ticagrelor and clopidogrel will be recalculated with these residual events allocated in different proportions to the treatment groups to assess the robustness of the results with regard to patients who are censored prior to the primary analysis censoring date.

Subgroup analysis 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 as the tests are exploratory and will be interpreted descriptively. Hazard ratios and 95% confidence intervals will be reported for each subgroup. Subgroup analyses will be performed on the primary efficacy and safety variables.

Subgroup analysis will be performed based on whether a patient had a prior MI (as defined in Section 4 and the eCRF) at baseline. In addition, the subgroup analysis will be performed based on a patient's Fontaine scale at baseline. Patients with Fontaine scale II will define one subgroup while patients with Fontaine scale III and IV will form the other. For the subgroup analysis of geographic regions, the four geographical regions will be:

- Europe/Africa
- Asia/Oceania
- North America
- Central/South America

Additional subgroup analyses will include age, sex, race, weight/BMI, prior antiplatelet therapy, medical history characteristics (eg, risk factors for developing atherothrombosis and risk factors for bleeding), revascularization history and history of coronary stent implantation.

Secondary efficacy variables

The analysis of the primary composite variable will be repeated for the secondary efficacy variables, which are in order

1. time from randomisation to first occurrence of any event in the composite of CV death, MI, ischemic stroke and ALI
2. time from randomisation to occurrence of CV death
3. time from randomisation to occurrence of MI
4. time from randomisation to occurrence of all-cause mortality
5. time from randomisation to occurrence of composite of CV death, MI, and all-cause Stroke (ischaemic or haemorrhagic)
6. time from randomisation to occurrence of ALI
7. time from randomisation to occurrence of lower extremity revascularization
8. time from randomisation to occurrence of any revascularisation (coronary, peripheral [limb, mesenteric, renal, carotid and other])

The analysis of the primary and the eight secondary efficacy variables will comprise the confirmatory analysis. In order to address the issue of multiple testing a hierarchical test sequence will be used.

Only if the treatment effect on the primary efficacy variable is significant at the 4.94% level, will the secondary efficacy variables be tested in a confirmatory sense in the order given above. The hypothesis testing will continue at the 4.94% significance level until the first statistically non-significant treatment difference ($p \geq 0.0494$) is observed. Secondary efficacy variables following in the sequence after the first non-significant test will be tested in an

exploratory manner. The results for objectives in Section 2.2 that are not part of the confirmatory analysis will be presented descriptively. Appropriate methods for time-to-event, continuous and categorical data will be used, with further details provided in the Statistical Analysis Plan. For objectives related to PROs further information is provided in Section 6.5, while for objectives related to Health Economics, further information can be found in Sections 6.9 and 11.3.

12.2.2 Safety variables

Analysis of time from first dose of study medication to each of the following endpoints will be performed

- the first TIMI major bleeding event (primary safety variable)
- the first TIMI major or minor bleeding event
- the first PLATO major bleeding event
- discontinuation of study medication due to any major bleeding event

The assessment of time to bleeding will focus on the items above but will also include analysis of time to first event for additional categories of bleeding according to the TIMI, PLATO, BARC and ISTH definitions. Treatment groups will be compared using the Cox proportional hazards model with a factor for treatment group. Kaplan-Meier estimates of the cumulative incidence of each event will be calculated and plotted and 95% confidence intervals for the hazard ratios presented. The safety assessment will also include analysis of total major bleeding events, fatal bleeding events, fatal or life threatening bleeding events, combined major and minor bleeding events across different categories as well as different categories of major and minor bleeding events separately. Exploration of potential risk factors for bleeding events, including subgroups and use of concomitant antithrombotic therapy, will be performed.

Bleeding events will be analyzed according to TIMI and PLATO bleeding definitions adjudicated by the CEC (see the CEC charter). BARC and ISTH bleeding profiles will be captured for each patient where appropriate but will not be formally adjudicated (Mehran 2011, Schulman 2005).

Non-serious AEs of interest, DAEs as well as SAEs will also be evaluated. MedDRA will be used for the coding and classification of AEs and SAEs in the database. AEs will be summarised by system organ class and preferred term using MedDRA. Summaries will be presented by treatment group using descriptive statistics. All AEs relating to bleeding will be summarised separately and the total number of bleeding events will be assessed. Exploration of potential risk factors for AEs that are increased with ticagrelor dosing may be done.

12.2.3 Interim analyses

The independent DMC will perform an interim analysis for potential early termination of the study for overwhelming efficacy, additional analyses may occur as defined in the DMC Charter. This interim analysis is planned after approximately 798 primary events have been adjudicated. A one-sided significance level of 0.001 (ie approximately 3 standard errors) will be used as criterion to consider stopping the study for overwhelming benefit of ticagrelor over clopidogrel. For early stopping the one-sided p-value must be less than 0.001 for the primary composite, as well as for CV Death alone. A one-sided significance level of 0.001 will be applied at each efficacy interim analysis. The Haybittle-Peto alpha spending function will govern the statistical testing at the final analysis to ensure an overall Type I error of 5% (East 5.2). If the planned interim analysis is performed when at least half of the total number of primary events have occurred and there are no additional interim analyses for efficacy, the significance level at the final analysis is at most 0.0494 (two-sided). If there are deviations from this plan the significance level at the final analysis will be adjusted according to the Haybittle-Peto alpha spending function. If the study is stopped at an efficacy interim analysis after having met the criteria for the primary composite endpoint and CV death, the testing of the remaining secondary endpoints will continue at the one-sided significance level 0.001. First CV death+MI+ischemic stroke+ALI will be tested and therafter variables 3-**8** in the sequence described in Section 12.2.1. There will be no futility stopping rule.

The DMC charter contains more information about the DMC procedures. A copy of the treatment codes will be made available to the statistician on the DMC. The Executive Committee and AstraZeneca will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each DMC meeting will be held in confidence by the DMC members until the end of the study when clean file and database lock are declared. Further details are given in the DMC charter.

12.2.4 Censoring

The Executive Committee will monitor the accrual of the number of primary events and when appropriate predict and define a primary analysis censoring date at which time the pre-defined target number of events for the primary composite endpoint are expected to have occurred.

The primary analysis censoring date will be the common date at which all patients who are event free for the given endpoint and have not withdrawn consent for participating in the study will be censored in efficacy time-to-event analyses. Events that occur after the primary analysis censoring date but before the ESTV will also be collected and adjudicated. These events may be included in sensitivity analyses but not in the primary analysis.

Patients who have not had the event(s) in question will be censored at the earlier of (1) the primary analysis censoring date and (2) the last study contact when all components of the endpoint in question were assessed. In the analysis of CV death and composites including CV death censoring will occur at the earliest of (1), (2) and the date of death from non-cardiovascular causes. For endpoints not including death, all deaths are censoring events.

Complete endpoint information will be pursued with every effort for all patients regardless of their study medication status, unless they exercise their right to withdraw consent. Patients who have a non-fatal event will continue study follow-up. For patients who withdraw consent and for whom only vital status (known to be alive at study closure, or date of death) may be obtained from public records, the occurrence of all components of the primary endpoint cannot be assessed. Thus the primary endpoint and its components ischaemic stroke, MI, and CV death will be censored at the time of consent withdrawal for those patients who withdraw consent and for whom only vital status is known from public records. However, the determination of all-cause mortality as a sole outcome event will utilise all publicly known mortality data, even that extending beyond date of consent withdrawal. The vital status information will be included in the analysis of all-cause mortality as a single secondary endpoint, in sensitivity analyses and tabulations.

Similarly, complete information on the primary endpoint may not be obtained for patients who are lost to follow-up (LTFU). Any such patient will be censored in the analysis of the primary composite endpoint at the last contact where all elements of the endpoint were assessed. A patient will not be recorded as LTFU until the end of the study, after every allowable effort to get in contact has been made. Hence, it is anticipated that the number of patients LTFU will be limited.

12.3 Determination of sample size

Based on clinical studies and epidemiological information, the event rate for the composite of CV death, MI and ischaemic stroke was estimated to be 7% per year in a population consisting of a spectrum of symptomatic PAD patients.

In the PLATO study a 16% RRR and 1.9% ARR (ticagrelor 9.8%, clopidogrel 11.7%) at one year were observed for the endpoint of CV death, MI and stroke. In the PAD subgroup in PLATO (data on file), a similar RRR of 15% was observed at higher absolute frequencies, ARR= 2.6% (18.0% vs. 20.6%). The RRR for ticagrelor versus clopidogrel in PLATO demonstrated consistency across multiple subgroups and consistency over time during the course of PLATO. In addition, results for the endpoint CV death, MI, and ischaemic stroke were similar to those obtained for CV death, MI, and stroke. With these considerations in mind a 15% RRR, which with 7% event rate corresponds to a 1.02% ARR per year, was assumed for the primary endpoint of CV death, MI, and ischaemic stroke of this study.

Assuming a 7% annual reference event rate and a HR of 0.85 over 18 months accrual period and anticipated 18 months of minimum follow-up, randomisation of approximately 11,500 patients **was** expected to yield 1596 primary endpoint events, which provide 90% power at a 4.94% significance level. Randomising an additional 2000 patients (i.e. target randomization approximately 13500 patients) would allow us to accrue the required 1596 primary endpoint events in approximately the above time frame if the clopidogrel event rate is 6%. For definition of the significance level at the final analysis, see Section 12.2.3. The sample size

was based on a test using the logrank statistic and was calculated using nQuery Advisor®[1] 7.0.

The observed aggregate event rate is currently estimated to be approximately 4.1%, and to conclude the study in a timely manner with maintained data quality, the number of targeted primary events will be reduced to a minimum of 1364, which will provide 85% power at 4.94% significance level. The sample size was again based on a test using the logrank statistic and was calculated using nQuery Advisor 7.0.

12.4 Independent Data monitoring committees

12.4.1 Clinical Event Adjudication Committee

An independent, blinded Clinical Event Adjudication Committee (CEC) will be appointed and will report to the DMC and Executive Committee.

The CEC will adjudicate all primary and secondary endpoints and bleeding events with the exception of occurrence of revascularization. The CEC charter details the precise responsibilities and procedures applicable for the CEC.

12.4.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be appointed and will report to the Executive Committee.

The DMC will be responsible for safeguarding the interests of the patients in the outcome study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. The DMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca/DCRI contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

[1] **NQuery Advisor is a registered trademark of Statistical Solutions, Saugus, MA, USA.**

In the case of a medical emergency the investigator should contact the EUCLID Study Physician or delegate via the clinical hotline.

Name	Role in the study	Address & telephone number
DCRI Medical Emergency Hotline	First line of communication for all medically relevant issues	Provided in study documentation
	DCRI EUCLID Study Team Physician	
	DCRI Associate Director	
	DCRI Project Lead	
	AstraZeneca Study Leader, responsible for global project management at central R&D centre	AstraZeneca R&D Pepparedsleden 1 SE-431 83 Mölndal
	AstraZeneca Study Team Physician, responsible for the protocol at central R&D centre	AstraZeneca R&D Pepparedsleden 1 SE-431 83 Mölndal

13.2 Overdose

An overdose of study medication is defined as intake of more than 4 yellow ticagrelor/placebo tablets or more than twice the prescribed dose of pink clopidogrel/placebo tablets a day.

In the event of an overdose of study medication ascertain the time and extent of the overdose regardless of severity. Determine the causative circumstance and whether haemorrhagic or toxic complications have occurred or are likely to do so. Depending on these facts it has to be decided if the patient should be hospitalised for observation or not. Bleeding is one of the most likely pharmacological effects of excessive ticagrelor dosing, and appropriate supportive measures such as volume replacement, local haemostatic measures, and decompression or drainage may be required depending on the extent of bleeding or volume of blood lost. Patients with overdose-related bleeding should be cautioned to avoid unnecessary activity, mechanical tissue stress, and minor trauma for at least 24 hours after the bleeding has stopped. For other symptoms that can be expected after an overdose of ticagrelor and additional information see the IB.

An overdose with associated AEs of interest or SAEs should be recorded. The SAE diagnosis/symptoms should be recorded on the relevant forms in the eCRF.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study medication occurs in the course of the study, then investigators or other centre personnel inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry centre.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 5 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study medication should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study medication under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other centre personnel inform appropriate AstraZeneca representatives **within 1 day,** ie, immediately but no later than **24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry centre within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

There are no restrictions against fathering a child when treated with ticagrelor. If paternal exposure pregnancy occurs in the course of the study, then investigators or other centre personnel should inform appropriate AstraZeneca representatives within 1 day as described in the maternal exposure Section 13.3.1.

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Clinical Study Protocol Appendix B

Drug Substance	Ticagrelor
Study Code	D5135C00001
Edition Number	1
Date	22 June 2012

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.>>

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
Drug Substance	Ticagrelor
Study Code	D5135C00001
Edition Number	1
Date	22 June 2012

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Ticagrelor
Study Code	D5135C00001
Edition Number	1
Date	22 June 2012

Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the patient meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a patient has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the appropriate AZ representative
  - Promptly enter the laboratory data into the CRF

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the patient **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the appropriate AZ representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the patient **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the appropriate AZ representative who will then inform the appropriate study personnel

The Astrazeneca Study Physician or delegate contacts the Investigator, to provide guidance, discuss and agree an approach for the study patient's follow-up and the continuous review of data.

The Investigator:

- Follows the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigates the etiology of the event and perform diagnostic investigations as discussed with the Astrazeneca Study Physician or delegate.

- Completes the Liver CRF Modules.

- If at any time (in consultation with the Astrazeneca Study Physician or delegate) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Management of Study Drug

Study drug should be discontinued if the patient develops clinical signs or symptoms of liver injury. However, if another cause is clear, it may be appropriate in some cases to continue treatment. Such a decision is entirely based on the judgment of the clinician responsible for the patient. However, the investigator should contact the Astrazeneca Study Physician or delegate to discuss the management of study drug whenever possible.

In general, study drug should be discontinued in the event of the laboratory findings listed below. However, other clinical situations may warrant study drug discontinuation and will be managed at the discretion of the investigator.

- ALT or AST >8xULN

- ALT or AST >5xULN for more than 2 weeks

- ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)

- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

1.4 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Astrazeneca Study Physician or delegate contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

For the purpose of this process a Hy's Law case is defined as:

Any patient with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg,

elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE or SAE will be made. If the alternative explanation is **not** an AE/SAE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term 'Hy's Law') according to standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

AstraZeneca

Amended Clinical Study Protocol Appendix E	
Drug Substance	Ticagrelor
Study Code	D5135C00001
Edition Number	1
Date	26 Sept 2013

Appendix E
EUCLID – Examining Use of tiCagreLor In paD

End Point Definitions

1. CLINICAL ENDPOINT DEFINITIONS

The following section provides the clinical endpoint definitions to be used in EUCLID. The definitions for death, MI, stroke, TIA, and unstable angina are based on the standardized draft definitions for end points (Hicks 2010). These definitions will be used by the clinical event adjudication committee to ensure consistent and standardized evaluation of potential endpoints in the trial**.**

1.1 Death

Deaths will be sub-classified by the adjudication committee as for the primary cause of either cardiovascular or non-cardiovascular primary cause.

Cardiovascular death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to an ischemic stroke, death due to other cardiovascular causes (e.g. dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention (other than one related to an acute MI), aortic aneurysm rupture, or peripheral artery disease), and deaths for which there was no clearly documented non-cardiovascular cause (presumed CV death). Any death with unknown/uncertain cause within 30 days of a stroke, MI or procedure/surgery will be considered a death due to the stroke, MI or procedure/surgery, respectively.

Non-cardiovascular death includes death due to respiratory failure, pneumonia, malignancy, trauma, suicide, infection/sepsis, multi-organ failure or any other clearly defined cause (e.g., liver failure or renal failure). Death due to gastrointestinal bleeding is considered a non-cardiovascular death.

Additionally, cardiovascular deaths will be sub-classified by coronary heart diseases (CHD) death and non-CHD death. CHD death includes Sudden Cardiac Death, Death due to Acute MI, and the subset of Death due to other Cardiovascular Causes that are secondary to a coronary revascularization procedure.

1.2 Definition of myocardial infarction

- For a spontaneous MI, detection of rise and/or fall of cardiac biomarkers, preferably troponin, with at least one value above the 99th percentile if available or or the upper reference limit (URL) from the local lab together with evidence of myocardial ischaemia with at least one of the following:
    - Clinical presentation consistent with ischaemia
    - ECG evidence of acute myocardial ischaemia
    - New pathological Q-waves
    - Autopsy evidence of acute MI

- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST-elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- Percutaneous Coronary Intervention-Related Myocardial Infarction: Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischaemia are not required.

    1. Biomarker elevations within 48 hours of PCI:

        – Troponin or CK-MB (preferred) >3 x URL *and*

        – No evidence that cardiac biomarkers were elevated prior to the procedure;

        OR

        Both of the following must be true:

            o ≥50%[1] increase in the cardiac biomarker result

            o Evidence that cardiac biomarker values were decreasing (eg, two samples 3 to 6 hours apart) prior to the suspected MI

    2. New pathological Q-waves

    3. Autopsy evidence of acute MI

- Coronary Artery Bypass Grafting-Related Myocardial Infarction:Peri- CABG MI is defined by the following criteria. Symptoms of cardiac ischaemia are not required.

    1. Biomarker elevations within 72 hours of CABG:

        – Troponin or CK-MB (preferred) >5 x URL *and*

        – No evidence that cardiac biomarkers were elevated prior to the procedure;

        OR

        – Both of the following must be true:

            o ≥ 50%[1] increase in the cardiac biomarker result

            o Evidence that cardiac biomarker values were decreasing (eg, two samples 3 to 6 hours apart) prior to the suspected MI.

[1] *Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.*

AND

2. One of the following:

   - New pathological Q-waves persistent through 30 days
   - New persistent non-rate-related LBBB
   - Angiographically documented new graft or native coronary artery occlusion
   - Other complication in the operating room resulting in loss of myocardium
   - Imaging evidence of new loss of viable myocardium

OR (regardless of items 1 and 2 above)

3. Autopsy evidence of acute MI

The definition of MI for this study intentionally excludes the category of silent MI.

1.3 Definition of stroke

A stroke is defined as a neurological deficit caused by an ischaemic or haemorrhagic central nervous system event without another cause leading to residual signs or symptoms lasting at least 24 hours after onset or leading to death.

Stroke will be further sub-classified as:

Ischaemic:

Ischemic stroke is defined as an infarction of the central nervous system tissue that results from a thrombus or embolus impairing central nervous system perfusion (and not primarily due to hemorrhage) with residual signs or symptoms lasting at least 24 hours after onset or leading to death. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke should be recorded as an ischemic stroke with hemorrhagic transformation rather than a hemorrhagic stroke event.

Haemorrhagic:

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction with a documented cause of intracranial hemorrhage on imaging (eg, computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) either in the cerebral parenchyma, or in the subdural, epidural or subarachnoid space with residual signs or symptoms at least 24 hours after onset or leading to death. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.

Unknown/No imaging performed: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy) but is judged to fulfill the stroke definition above, the stroke will be classified as ischaemic for purposes of the study.

1.4 Definition of revascularisation

A revascularization procedure is an endovascular or open surgical procedure designed to improve blood flow to an organ or body part. Revascularization procedures will be classified as elective or non-elective. Revascularization procedures will be further sub-classified as:

a. Ischemia-driven (or clinically-driven) coronary artery revascularization

    i. Type of procedure

        1. Surgical revascularization (i.e. CABG)

        2. Percutaneous revascularization (i.e. PCI)

        3. Other (i.e. hybrid)

b. Peripheral artery revascularization

    i. Type of procedure

        1. Surgical revascularization (i.e. arterial bypass surgery, endarterectomy, thromboembolectomy)

        2. Endovascular revascularization (i.e. angioplasty, atherectomy, stenting, thromboembolectomy)

        3. Other (i.e. hybrid)

    ii. Location of procedure

            1. Aorto-iliac

            2. Femoral, popliteal, tibial

                a. Procedure performed due to intermittent claudication

                b. Procedure performed due to critical limb ischemia

                c. Procedure performed due to other indication (i.e. vascular complication from prior procedure)

            3. Carotid

4. Mesenteric

5. Renal

1.5 Definition of unstable angina

1. Symptoms of myocardial ischaemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG

      - ST elevation

        New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

      - ST depression and T-wave changes

        New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

      The above ECG criteria illustrate patterns consistent with myocardial ischaemia. It is recognised that lesser ECG abnormalities may represent an ischaemic response and may be accepted under the category of abnormal ECG findings.

   b. Definite evidence of myocardial ischaemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischaemic symptoms/signs

   c. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischaemic symptoms/signs

   d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial

ischaemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

1.6 Definition of transient ischaemic attack (TIA)

Transient ischaemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, *without* evidence of acute infarction. Neurological symptoms from a TIA resolve spontaneously within 24 hours without deficit, unlike an acute ischaemic stroke. For inclusion in the secondary composite efficacy endpoint the TIA must either require hospitalization if an outpatient or prolonged hospitalization if an inpatient.

1.7 Definition of major amputation due to PAD

Major amputation due to PAD is defined as loss of a peripheral part of the lower limb at or above the ankle.

Minor amputation due to PAD is defined as loss of any part of the foot.

1.8 Definition of Acute Limbic Ischemia requiring hospitalization

Acute limb ischemia is defined as:

- clinical history of a rapid or sudden decrease in limb perfusion

and either

- new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis

or

confirmation of arterial obstruction by imaging, intra-operative findings or pathological evaluation including amputation findings.

2. BLEEDING DEFINITIONS

The CEC will adjudicate and evaluate bleeding events (excluding minimal) according to the following bleeding definitions: TIMI and PLATO. BARC and ISTH bleeding profiles will be captured for each patient where appropriate but will not be formally adjudicated (Mehran 2011, Schulman 2005).

2.1 Thrombolysis In Myocardial Infarction Study Group (TIMI)

2.1.1 Non-CABG related bleeding

2.1.1.1 Major

- Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
- Fatal bleeding (bleeding that directly results in death within 7 d)

2.1.1.2 Minor

- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

2.1.1.3 Requiring medical attention

- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
- Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
- Leading to or prolonging hospitalization
- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

2.1.1.4 Minimal

- Any overt bleeding event that does not meet the criteria above

2.1.1.5 Bleeding in the setting of CABG

- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding

- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output > 2 L within a 24 hour period

2.2 A study of PLATelet inhibition and patient Outcomes (PLATO)

2.2.1 Major life-threatening

- Fatal
- Intracranial
- Intrapericardial with cardiac tamponade
- Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
- Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
- Requiring transfusion of ≥4 U whole blood or PRBCs

2.2.1.1 Other major

- Significantly disabling (eg, intraocular with permanent vision loss)
- Associated drop in hemoglobin of 3 to 5 g/dL
- Requiring transfusion of 2 to 3 U whole blood or PRBCs

2.2.1.2 Any major

- Any one of the above criteria

2.2.2 Minor

- Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)

2.2.3 Minimal

- All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment

2.3 Bleeding Academic Research Consortium (BARC)

2.3.1 Type 0

- No bleeding

2.3.2 Type 1

- Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

2.3.3 Type 2

- Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

2.3.4 Type 3

2.3.4.1 Type 3a

- Overt bleeding plus hemoglobin drop of 3 to <5 g/dL[*] (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

2.3.4.2 Type 3b

- Overt bleeding plus hemoglobin drop ≥5 g/dL[*] (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

2.3.4.3 Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

2.3.5 Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period[†]
- Chest tube output ≥2L within a 24-h period

2.3.6 Type 5: fatal bleeding

2.3.6.1 Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

2.3.6.2 Type 5b

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

2.4 International Society on Thrombosis and Harmonisation (ISTH)

2.4.1 Major Bleeding

- with a fall in hemoglobin of ≥2 g/dL, or
- with transfusion of ≥2 units of PRBC or whole blood, or
- that occurs in a critical location, i.e., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or
- that causes death

2.4.2 Clinically Relevant Non-Major Bleeding

- that does not meet criteria for major bleeding, and
- that requires any medical or surgical intervention to treat the bleeding

3. REFERENCES

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