AstraZeneca

Revised Clinical Study Protocol

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A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor twice daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus

[THEMIS - Effect of Ticagrelor on Health Outcomes in diabEtes Mellitus patients Intervention Study]

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	11 May 2015		
2	23 September 2015		
3	7 February 2017		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	6 February 2014		
2	19 June 2014		

PROTOCOL SYNOPSIS

A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor twice daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus

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International Co-ordinating Investigators

Study centres and number of patients planned

This study will be conducted at approximately 1200 study centres in about 40 countries worldwide. It is expected that approximately 19000 patients will be randomised to study treatment.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2014	Phase IIIb
Estimated date of last patient completed	Q4 2018	

Objectives

Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor twice daily (bd) vs. placebo for the prevention of major cardiovascular (CV) events (composite of CV death, myocardial infarction [MI] or stroke) in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke.

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown etiology).

Secondary objectives

The secondary objectives of the study (presented in hierarchical order) are to compare the effect of long-term treatment with ticagrelor vs. placebo for:

1. Prevention of CV death. The efficacy variable is time from randomisation to death of CV cause

2. Prevention of MI. The efficacy variable is time from randomisation to first occurrence of MI

3. Prevention of ischaemic stroke. The efficacy variable is time from randomisation to first occurrence of ischaemic stroke

4. Prevention of all-cause death. The efficacy variable is time from randomisation to death of any cause.

Exploratory objectives

Other objectives are to explore other long-term treatment effects of ticagrelor vs. placebo on:

- Prevention of the composite of all-cause death, MI or stroke. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause death, MI or stroke
- Prevention of stroke. The efficacy variable is time from randomisation to first occurrence of stroke
- Effect on irreversible harm events, the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding
- Health care resource utilisation and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire to support health technology assessment and health economic modelling.

Safety objectives

The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo in patients with T2DM at high risk of CV events, with or without background low-dose ASA therapy. Bleeding events will be analyzed using the Thrombolysis in Myocardial Infarction Study Group (TIMI) definitions, those used in the PLATO (PLATelet inhibition and patient Outcomes) study, and the Bleeding Academic Research Consortium (BARC) definitions. 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 permanent discontinuation of study medication due to any bleeding event.

Non-serious AEs of interest (ie, dyspnoea, renal impairment, bradyarrhythmia, gout, and pneumonia), adverse events that leads to permanent discontinuation of study medication (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug.

Study design

This is an event-driven, randomised, double blind, placebo controlled, parallel group, international multi-centre study to evaluate the effect of ticagrelor bd vs. placebo for prevention of major CV events in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke. Patients will be managed consistent with local standard of care including provision of dietary and lifestyle advice according to local diabetes treatment guidelines. Patients should be treated with low-dose acetylsalicylic acid (ASA)/AspirinTM 75 150 mg once daily (od), unless contraindicated or not tolerated, in accordance with national and international clinical practice guidelines.

Target patient population

Men and women ≥50 years of age with T2DM at high risk of CV events, but without a medical history of previous MI or stroke.

Study medication, dosage and mode of administration

Ticagrelor bd given orally or corresponding placebo. Initially ticagrelor 90 mg or corresponding placebo was the selected dose, but reduced to ticagrelor 60 mg or corresponding placebo in Clinical Study Protocol Amendment No 1.

Duration of treatment

The study is event-driven and 19000 randomised patients are estimated to be required in order to collect 1385 adjudicated primary endpoint events. The anticipated maximal duration of treatment with study medication for an individual patient is 58 months. However, the actual duration of the study will be based on accrual of the pre-determined number of adjudicated primary endpoint events, and therefore the final treatment time may be shorter or longer than 58 months. The expected minimum follow-up period is 29 months and the expected average follow-up period is 40 months, based on an enrolment period of 28 months.

Statistical methods

All efficacy analyses will be based on the intention to treat (ITT) principle using the full analysis set (FAS) including only adjudicated endpoint events. For time to event variables, treatments will be compared using a Cox proportional hazards model with a factor for treatment group. The p-value, hazard ratio (HR) and 95% confidence interval will be reported. Kaplan-Meier estimates of the cumulative risk will also be presented. The family wise error rate will be controlled for the primary and secondary efficacy analyses by applying a hierarchical test sequence.

The final primary treatment comparison will be made at a significance level of 4.96%, adjusted for the planned efficacy interim analysis. Assuming a true hazard ratio of 0.84 between ticagrelor and placebo, 1385 primary endpoint events will provide a power of 90%. With an annual event rate of 2.5% in the placebo treatment group, 19000 patients, randomised in a 1:1 ratio, are estimated to provide the required number of primary events after receiving study medication for an anticipated average of 40 months.

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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
ACS	Acute Coronary Syndrome
ACCEPT-D	Study acronym - Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes
ACCF	American College of Cardiology Foundation
Adjudicated endpoint event	An event that fulfils study specific endpoint criteria as confirmed during adjudication by the independent CEC
ADA	American Diabetes Association
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ARR	Absolute Risk Reduction
ASA	Acetylsalicylic acid/Aspirin™
ASCEND	Study acronym - A Study of Cardiovascular Events iN Diabetes
AST	Aspartate aminotransferase
AUC	Area under the curve
BARC	Bleeding Academic Research Consortium
bd	Twice daily dosing
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CAPRIE	Study acronym – Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events
CCU	Coronary Care Unit
CHD	Coronary Heart Disease
CHARISMA	Study acronym – Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance
CEC	Clinical Endpoint Committee
CI	Confidence Interval

Abbreviation or special term	Explanation
CRF	Case Report Form (electronic/paper)
C_{max}	Maximum free plasma concentration
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular Disease
CYP450	Cytochrome P450
DAE	Discontinuation of Study medication due to Adverse Event
DCCT	Diabetes Control and Complication Trials
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
EASD	European Association for the study of Diabetes
EC	Executive Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	Euro Quality of Life – 5 dimensions
EUCLID	Study Acronym -Examining Use of tiCagreLor In paD
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GPIIb/IIIa	Glycoprotein IIb/IIIa
GRand	AstraZeneca Global Randomisation system
HbA1c	Haemoglobin A1c
HECON	Health Economics
HR	Hazard Ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IFCC	International Federation of Clinical Chemistry
ICU	Intensive Care Unit

Abbreviation or special term	Explanation
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 internationally.
IPA	Inhibition of platelet aggregation
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LMWH	Low-molecular-weight heparin
LTFU	Lost To Follow-Up
LVH	Left Ventricular Hypertrophy
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NSAID	Non Steroidal Anti-Inflammatory Drug
od	Once daily
PACD	Primary Analysis Censoring Date
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamics
PEGASUS	Study Acronym – PrEvention with ticaGrelor of secondAry thrombotic events in high riSk patients with prior acUte coronary Syndrome
PI	Principal Investigator
PLATO	Study Acronym – a study of PLATelet inhibition and patient Outcomes
Potential endpoint event	An event submitted to the independent CEC for adjudication in relation to study specific endpoint criteria
PPI	Proton Pump Inhibitor
PRO	Patient Reported Outcomes
PTDV	Premature Treatment Discontinuation Visit
RRR	Relative Risk Reduction

Abbreviation or special term	Explanation
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
TBL	Total Bilirubin
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis In Myocardial Infarction
T2DM	Type 2 Diabetes Mellitus
UFH	Unfractionated heparin
ULN	Upper Limit of Normal
URL	Upper Reference Limit
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Cardiovascular disease (CVD), which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (PAD), is the leading cause of death in most developed countries. In the United States, CVD accounted for approximately 1 of every 3 deaths in 2009 (Go et al 2013). The totality of evidence from basic research, clinical investigations, observational epidemiologic studies, and randomised clinical trials has provided strong support for the net benefits of acetylsalicylic acid (ASA)/Aspirin™ in decreasing the risk of CVD events in a wide range of patients with established CHD (Antithrombotic Trialists' Collaboration 2002). Diabetes substantially increases the risk of major cardiovascular (CV) complications in patients with and without established CVD (Preis et al 2009, Bhatt et al 2010) such that most patients with diabetes die of CV diseases (Roger et al 2011).

1.1.1 Medical need

Diabetes mellitus (DM) is commonly associated with macrovascular complications, clinically resulting in premature CHD and increased risk of cerebrovascular disease (Vazzana et al 2012). Patients with Type 2 DM (T2DM) have an increase in the risk of CHD (Schramm et al 2008, Krempf et al 2010), and patients with DM but without previous myocardial infarction (MI) carry the same level of risk for subsequent acute coronary events as patients without DM but with previous MI (Haffner et al 1998). Several mechanisms contribute to this increased risk. There are common coexisting CV risk factors in patients with DM, eg, hypertension, dyslipidaemia, obesity and renal dysfunction, as well as a diabetic prothrombotic state, including endothelial dysfunction, impaired fibrinolysis, increased levels of coagulation factors and platelet hyperreactivity (Angiolillo and Suryadevara 2009).

1.1.2 Role of antiplatelet therapy in patients with DM

Based on meta-analyses, antiplatelet agents are recommended for patients with established CHD with or without DM (Antithrombotic Trialists' Collaboration 2002, Antithrombotic Trialists' Collaboration 2009), while the benefits and risks of ASA for primary prevention of atherotrombotic events in patients with DM remains a matter of debate (Mehran et al 2011). In a recent meta-analysis (De Berardis et al 2009), patients with DM derived less benefit from ASA than expected. ASA compared to placebo did not achieve a statistically significant reduction in the risk of major CV events; in subgroup analysis ASA significantly reduced the risk of MI in men but not in women. The uncertainty on benefit risk relation using ASA in this patient population is also illustrated by inconsistent international guidelines and updates without any major new data available (Buse et al 2007, Rydén et al 2007, Pignone et al 2010, Rydén et al 2013). Due to the remaining uncertainty regarding the benefit of ASA for primary prevention of CV events in patients with DM, two randomised controlled trials are currently evaluating ASA in patients with T2DM. The ongoing ACCEPT-D trial evaluates the safety and efficacy of ASA at the dose of 100 mg vs. no ASA in 5170 patients with DM (De Berardis et al 2007). The ASCEND trial evaluates the effect of ASA vs. placebo in more than 15000 patients with DM and is expected to report in 2017.

One of the hypotheses for the poor efficacy of ASA in patients with DM is that they have a rapid platelet turnover, and that administration of ASA once a day may not be sufficient to effectively inhibit thromboxane generation. This is supported by several small pharmacodynamic and pharmacokinetic studies (DiChiara et al 2007, Addad et al 2010, Capodanno et al 2011, Smith et al 2011, Spectre et al 2011, Henry et al 2011).

1.1.3 Product background

Ticagrelor is an orally active, reversibly binding, selective P2Y12 adenosine diphosphate (ADP) receptor antagonist that prevents ADP mediated platelet activation and aggregation. Ticagrelor 90 mg twice daily (bd) dosing has greater platelet inhibition than clopidogrel 75 mg once daily (od). Unlike clopidogrel, ticagrelor does not require metabolic activation. As a result, ticagrelor provides greater and more consistent interpatient antiplatelet effect (Htun and Steinhubl 2013).

No dosing adjustment is needed in patients with renal impairment. No dose adjustment is needed for patients with mild hepatic impairment. Cmax and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the Inhibition of Platelet Activation (IPA) effect of ticagrelor was similar between the two groups. Caution is advised in patients with moderate hepatic impairment because ticagrelor has not been studied in these patients. Use of ticagrelor is contraindicated in patients with severe hepatic impairment.

In the pivotal PLATO study of 18624 acute coronary syndrome (ACS) patients, ticagrelor was superior to clopidogrel in reducing the rate of the composite efficacy endpoint of CV death, MI, and stroke (RRR 16%, ARR 1.9%; HR 0.84 [95% CI 0.77, 0.92]; p=0.0003) for up to 12 months of treatment. Ticagrelor reduced CV death (HR 0.79, 95% CI 0.69, 0.91; p= 0.0013) and all-cause mortality (HR 0.78, 95% CI .69, 0.89; nominal p =0.0003) compared with clopidogrel (Wallentin et al 2009). There was no difference as to PLATO defined major bleeding, but compared to clopidogrel, patients treated with ticagrelor experienced an increase in combined major and minor bleeding, and more major bleeding unrelated to procedures. Dyspnoea occurred more commonly with ticagrelor compared to clopidogrel. In a subgroup analysed with Holter monitoring, there was a higher incidence of ventricular pauses observed during the first week. Pauses were rarely associated with symptoms; the two treatment groups did not differ significantly with respect to the incidence of syncope or pacemaker implantation. The levels of creatinine and uric acid increased slightly more during the treatment period with ticagrelor than with clopidogrel (Wallentin et al 2009). In addition, pulmonary AEs like pneumonia less often resulted in death in the ticagrelor group (Storey et al 2013).

Further information regarding the background, pharmacological class, properties, and mechanism of action of ticagrelor can be found in the current Investigator's Brochure (IB).

1.1.4 Ticagrelor in patients with DM

Ticagrelor effectively inhibits platelet function in patients with T2DM. In patients with T2DM with ongoing ACS, ticagrelor achieves a high platelet inhibition, and effectively treats high platelet reactivity (Alexopoulos et al 2013).

In the PLATO subgroup of patients with DM (4662 patients including 1036 patients on insulin), the benefits and risks of ticagrelor were consistent with the overall study results; ticagrelor reduced the primary composite endpoint of CV death, MI or stroke (HR 0.88, 95% C 0.76, 1.03) and all-cause mortality (HR 0.82, 95% CI 0.66–1.01) with no increase in total major bleeding. There was no heterogeneity between patients with or without ongoing insulin treatment (James et al 2010).

1.2 Research hypothesis

This study is designed to test the hypothesis that ticagrelor is superior to placebo, in prevention of major CV events, as measured by time to first event of the composite of CV death, MI, or stroke in patients with T2DM at high risk of CV events.

1.3 Rationale for conducting this study

Presently neither ASA, nor any ADP receptor antagonist, are indicated specifically for prevention of CV events in patients with DM without previous MI or stroke. However, diabetic patients with documented coronary artery stenosis are generally considered to be at high CV risk and antiplatelets should be used unless contraindicated or not tolerated (Rydén et al 2013, Smith et al 2011).

In the CAPRIE trial, patients with DM and previous MI, stroke or PAD were found to derive more benefit from clopidogrel than from ASA (CAPRIE Steering Committee 1996, Bhatt et al 2002), indicating that potent antiplatelet therapy is useful among patients with DM.

Although the CHARISMA trial failed to meet its primary study endpoint, patients with T2DM and previous MI/established CHD, stroke or PAD also suggested a reduction in CV events when antiplatelet therapy was intensified from ASA alone to ASA and clopidogrel (Bhatt et al 2002, Bhatt et al 2006).

Ticagrelor has several potential advantages as an oral antiplatelet agent for prevention of CV events in patients with T2DM but without a medical history of previous MI or stroke. Ticagrelor requires no metabolic activation, providing a rapid onset and a consistent interpatient antiplatelet effect. It is a more powerful antiplatelet agent than both ASA and clopidogrel, and it inhibits erythrocyte adenosine uptake hypothesized to promote preconditioning, decrease infarct size and possibly prevent sudden cardiac death (Htun and Steinhubl 2013). The reversible binding of ticagrelor on the P2Y12 ADP receptor and the bd dosing would address concerns with ASA or thienopyridines of insufficient platelet inhibition related to rapid platelet turnover (Henry et al 2011).

Patients with T2DM and documented coronary artery atherosclerosis have a particularly high risk of major CV events and could potentially benefit from ticagrelor.

The current study is designed to evaluate the effects of ticagrelor on MI, stroke, CV death and bleeding events in the long-term management of patients with T2DM at high risk of CV events.

1.4 Benefit/risk and ethical assessment

Currently, the benefit of ASA is well documented for secondary prevention following a CV event irrespective of diabetes status. However, evidence for use of ASA in prevention of CV events in patients with T2DM without prior MI is unclear as reflected by differences in recommendations given by treatment guidelines and current position papers (Buse et al 2007, Rydén et al 2007, Pignone et al 2010, Rydén et al 2013).

T2DM is associated with multiple factors promoting macrovascular and microvascular disease including increased atherothrombotic CHD risk, demonstrating an unmet need for well-tolerated and effective antithrombotic treatment in patients with T2DM and at high risk of CV events, including those without prior MI or stroke. Among patients receiving local standard of care including lifestyle counselling and risk factor management, a placebo controlled study allowing individualized concomitant low dose ASA is warranted and justified.

More than 25,000 healthy subjects or patients have been exposed to ticagrelor in the completed phase I, II, III and IV studies and the overall conclusion based on these studies is that Ticagrelor reduces the risk of recurrent thrombotic events and is generally well tolerated. The key large, international Phase III studies were PLATO (D5130C05262) and PEGASUS (D5132C00001).

In PLATO, ticagrelor demonstrated superiority to clopidogrel in the prevention of thrombotic events (relative risk reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, number needed to treat [NNT] = 54) of the composite efficacy endpoint (CV death, MI, and stroke) over 12 months. The difference in treatments was driven by CV death and MI with no difference on strokes. Ticagrelor demonstrated a statistically significant RRR of 16% (ARR 1.1%) for MI and a 21% RRR (ARR 1.1%) for CV death. The treatment effect of ticagrelor over clopidogrel appeared consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA). The treatment effect was evident early (ARR 0.6% and RRR of 12% at 30 days), with a constant treatment effect over the entire 12 month period, suggesting it is appropriate to treat for at least 12 months.

In PEGASUS, Both the 90 mg and 60 mg regimens of ticagrelor were superior to placebo, both in combination with ASA, in the prevention of thrombotic events (composite efficacy endpoint: CV death, MI and stroke), with a consistent treatment effect over the entire study period, yielding a 15% RRR and 1.2% ARR at 36 months for ticagrelor 90 mg and a 16% RRR and 1.3% ARR at 36 months for ticagrelor 60 mg. Each of the components of the composite endpoint contributed to the treatment effect (CV death 13% and 17% RRR; MI

19% and 16% RRR; stroke 18% and 25% RRR; for ticagrelor 90 mg and 60 mg, respectively). This effect was consistent throughout the study, with duration of treatment up to 48 months (median 33 months). The treatment effect was consistent across most pre-defined patient subgroups, including patients with diabetes mellitus; the differences observed in hazard ratio point estimates across subgroups were as expected given the large number of patient characteristics analysed.

The most commonly reported adverse events in ticagrelor-treated patients in both PLATO and PEGASUS were bleeding and dyspnoea. 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. There were few fatal bleeding events in the study, 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on ticagrelor than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between ticagrelor and clopidogrel. Bleeding occurred with similar frequency in the ticagrelor and clopidogrel groups independent of DM status (James et al 2010).

In PEGASUS, TIMI Major bleeding for ticagrelor was higher than for placebo, both on a background of ASA consistent in patients with or without diabetes. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed for intracranial haemorrhage (ICH), as compared to placebo. There were few fatal bleeding events in the study, 6 (0.1%) for ticagrelor 90 mg, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for placebo. Therefore, the observed increased risk of TIMI Major bleeding with ticagrelor was primarily due to a higher frequency of Other TIMI Major bleeding (ie, excluding ICH and fatal bleeding) driven by events in the gastrointestinal System Organ Class.

Adverse events other than bleeding and dyspnoea observed across these 2 studies in adult patients given ticagrelor include small increases in serum creatinine, increased serum uric acid concentrations, gout, and higher event rates for terms related to dizziness, hypotension, and syncope on ticagrelor compared with placebo; however, these latter events were not associated with an increase in events of bradyarrhythmia.

Efficacy and safety will be monitored by an independent Data Monitoring Committee (DMC).

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to compare the effect of long-term treatment with ticagrelor bd vs. placebo for the prevention of major CV events (composite of CV death, MI or stroke) in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke.

The primary efficacy variable is time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown etiology).

2.2 Secondary objectives

The secondary objectives of the study (presented in hierarchical order) are to compare the effect of long-term treatment with ticagrelor vs. placebo for:

1. Prevention of CV death. The efficacy variable is time from randomisation to death of CV cause

2. Prevention of MI. The efficacy variable is time from randomisation to first occurrence of MI

3. Prevention of ischaemic stroke. The efficacy variable is time from randomisation to first occurrence of ischaemic stroke

4. Prevention of all-cause death. The efficacy variable is time from randomisation to death of any cause.

2.3 Exploratory objectives

Other objectives are to explore other long-term treatment effects of ticagrelor vs. placebo on:

- Prevention of the composite of all-cause death, MI or stroke. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all- cause death, MI or stroke

- Prevention of stroke. The efficacy variable is time from randomisation to first occurrence of stroke

- Effect on irreversible harm events, the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding

- Health care resource utilisation and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire to support health technology assessment and health economic modelling.

2.4 Safety objective

The overall safety objective of this study is to assess the safety and tolerability of long-term therapy with ticagrelor compared to placebo in patients with T2DM at high risk of CV events, with or without background low-dose ASA therapy. Bleeding events will be analyzed using the Thrombolysis in Myocardial Infarction Study Group (TIMI), PLATO (PLATelet

inhibition and patient Outcomes), and the Bleeding Academic Research Consortium (BARC) definitions. 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 permanent discontinuation of study medication due to any bleeding event.

Non-serious AEs of interest (ie, dyspnoea, renal impairment, bradyarrhythmia, gout, and pneumonia), adverse events that leads to permanent discontinuation of study medication (DAEs) and all serious adverse events (SAEs) will be reviewed within the context of the earlier safety experience with the drug.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is an event-driven, randomised, double blind, placebo controlled, parallel group, international multi-centre study to evaluate the effect of ticagrelor bd vs. placebo for prevention of major CV events in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke. Approximately 19000 patients at approximately 1200 study centres in about 40 countries will be randomised (1:1) to receive either ticagrelor bd or placebo bd. Patients will be managed consistent with local standard of care including dietary and lifestyle advice (see Appendix C). Patients should be treated with low-dose ASA 75-150 mg od, unless contraindicated or not tolerated, in accordance with national and international clinical practice guidelines. The study design is shown in Figure 1.

The study is designed and will be directed and published by an Executive Committee (EC [see Section 5.10.1]). The following additional committees will be selected: an independent Data Monitoring Committee (DMC) (see Section 5.10.4) an International Steering Committee (see Section 5.10.2) and a Clinical Endpoint Committee (CEC) (see Section 5.10.3).

Duration of treatment

The study is event-driven and 19000 randomised patients are estimated to be required in order to collect 1385 adjudicated primary endpoint events. The anticipated maximal duration of treatment with study medication for an individual patient is 58 months. However, the actual duration of the study will be based on accrual of the pre-determined number of adjudicated primary endpoint events, and therefore the final treatment time may be shorter or longer than

58 months. The expected minimum follow-up period is 29 months and the expected average follow-up period is 40 months, based on an enrolment period of 28 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 adjudicated primary endpoint events (1385).

As an interim analysis for efficacy is planned and 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.

Visit 1 - Enrolment (7 ± 7 days prior to randomisation)

All potentially eligible patients will undergo an enrolment visit after the informed consent form has been signed. Eligibility criteria including relevant medical and surgical history will be reviewed. Demography, vital signs (pulse and BP), and weight and height will be assessed. Dietary and life-style advice will be given according to local diabetes treatment guidelines. Women of childbearing potential will be tested for pregnancy.

Visit 2 - Randomisation (Day 0)

The enrolment visit (Visit 1) and randomisation visit (Visit 2) should preferably be separated by at least 7 days (mandatory for women of childbearing potential) and up to a maximum of 14 days but can be combined into one single visit given that the patient has had sufficient time to consider study information, and that all information necessary to assess eligibility is available.

Men and women ≥50 years of age with T2DM at high risk of CV events, but without a medical history of previous MI or stroke, fulfilling all of the inclusion criteria (see Section 4.1) and none of the exclusion criteria (see Section 4.2) can be randomised into the study (there can be no exceptions to this rule).

For patients randomised into the study, vital signs (pulse and BP) and an electrocardiogram (ECG) including assessment of heart rate will be obtained. Blood samples for local laboratory analysis (baseline) will be taken preferably after 6 hours fasting, if not already collected within previous 30 days (See Section 6.4.6). Detailed recording of all concomitant medications (baseline recording) will be made. (NB. Post randomisation (except for the study closure visit), detailed recording of concomitant medication only includes ASA and ADP receptor antagonist use and any medication given in association with SAEs and potential endpoint events, from one month prior to start date of the event until one month post start date of the event). Patients will complete the EQ-5D form. The urine pregnancy test will be repeated for women of childbearing potential. Dietary and lifestyle advice will be provided to the patients according to local diabetes treatment guidelines. Study medication will be dispensed. SAEs will be recorded.

Visit 3 and 4 - scheduled telephone contacts 7 and 30 days after randomisation

At visit 3 and 4 (telephone contacts) AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. A compliance reminder regarding study medication will be given.

Visit 5 - On-site visit 3 months after randomisation

At visit 5 (on-site visit), AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. The patient will return study medication dispensed at the previous on-site visit (visit 2). New study medication will be dispensed and drug accountability of the returned medication will be checked. A compliance reminder regarding study medication will be given and dietary and lifestyle advice will be provided according to local diabetes treatment guidelines.

Visit 6, 8, 10, 12, 14 etc. - On-site visits 6, 12, 18, 24, 30 months etc. after randomisation

During the scheduled on-site visits every 6 months after randomisation, AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. The patient will complete the EQ-5D form and return study medication dispensed at the previous on-site visit. New study medication will be dispensed and drug accountability of the returned medication will be checked. A compliance reminder regarding study medication will be given and dietary and lifestyle advice will be provided according to local diabetes treatment guidelines.

Visit 7, 9, 11, 13 etc. - Scheduled telephone contacts at 9, 15, 21, 27 months etc. after randomisation

During the scheduled phone contacts AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. A compliance reminder regarding study medication will be given.

Unscheduled visits

An unscheduled visit may occur in-between scheduled visit eg, to follow-up on potential endpoint events.

Study Closure Visit (SCV)

When the predetermined number of adjudicated primary endpoint events is anticipated, the Primary Analysis Censoring Date (PACD) will be declared by the EC (see Section 12.2.4). All randomised patients (including any patients who have discontinued treatment with study medication and thus attended a Premature Treatment Discontinuation Visit [PTDV]) should return for their SCV as soon as possible but no later than 2 months (60 days) after the PACD. The actual time-window agreed for individual sites will depend on eg, the number of patients per site.

AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. The patient will complete the EQ-5D form and return study medication (if not returned at a PTDV). Vital signs (pulse and BP) will be assessed and detailed recording of all concomitant medication will be made. Drug accountability of the returned medication will be checked.

Study patients will be instructed to discontinue study medication but to continue low-dose ASA if clinically indicated and as judged by the investigator according to individual risk

evaluation and local standard of care. Patients currently on open-label treatment with an ADP receptor antagonist (see Section 5.6.3.3), should continue on this treatment for as long as medically indicated and in accordance with local medical guidelines and standard of care.

All randomised patients, whether taking study medication or not, should be followed up at the end of the study at a minimum for CV events and survival. In cases where patients have withdrawn consent, survival based on publicly available sources will be investigated at the study end, in accordance with local regulations.

The study flow chart is shown in Figure 1 and the assessment schedule in Table 1.

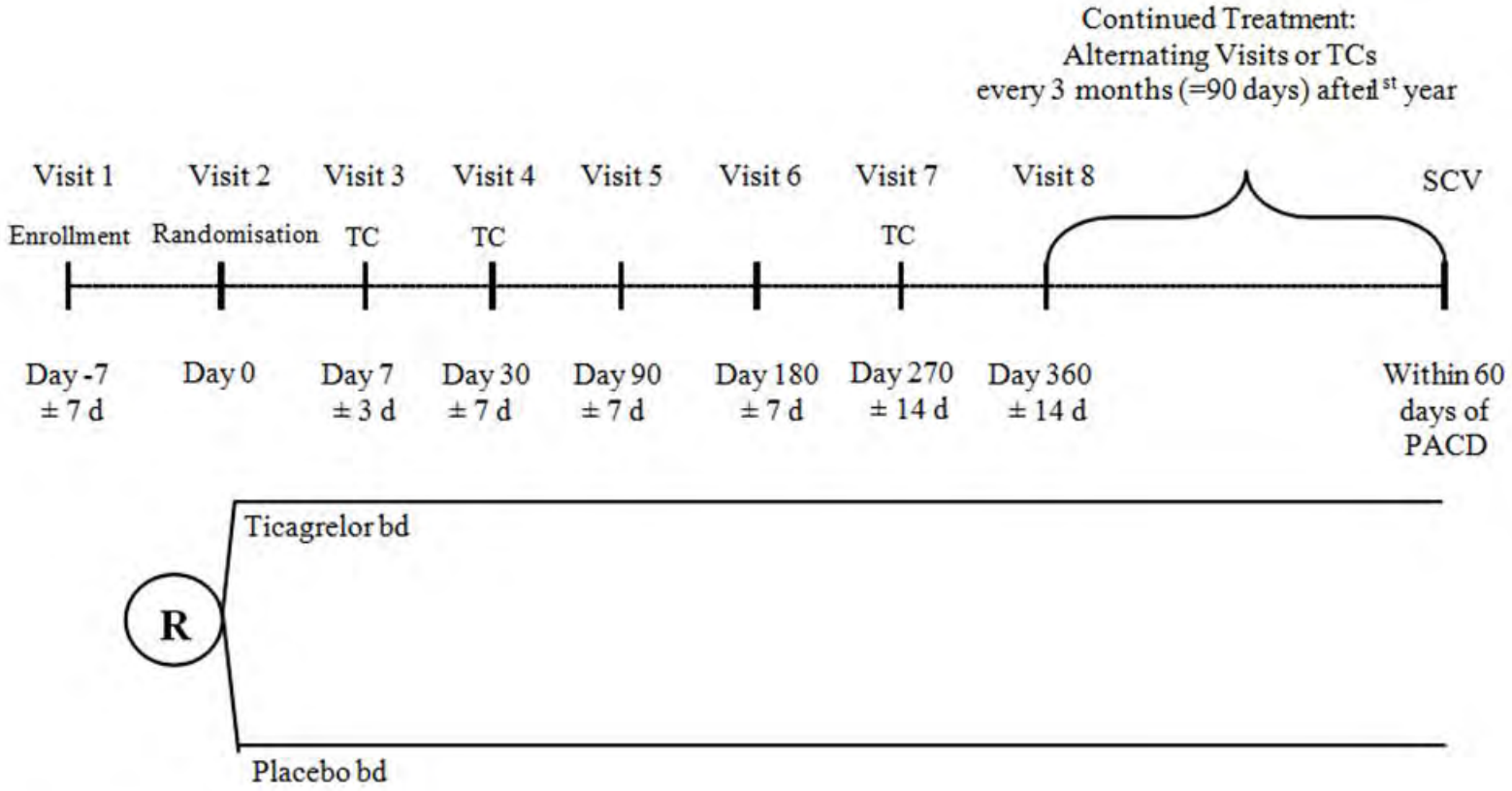
Premature Treatment Discontinuation Visit (PTDV)

Patients who prematurely and permanently discontinue treatment with study medication 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. AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs will be recorded. The patient will complete the EQ-5D form and return study medication dispensed at the previous on-site visit. Drug accountability of the returned medication will be checked and vital signs (pulse and BP) will be assessed. Dietary and lifestyle advice will be provided according to local diabetes treatment guidelines.

Patients who discontinue treatment prematurely still need to attend the Study Closure Visit (SCV).

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



TC = Telephone Contact
R = Randomisation
SCV = Study Closure Visit
PACD = Primary Analysis Censoring Date (eg, date when the predetermined number of adjudicated primary events are anticipated)
bd = twice daily

Table 1 Assessment Schedule

	Visit 1 Enrol-ment[a]	**Visit 2 Rando-misation[a]**	**Visit 3 TC[b]**	**Visit 4 TC**	**Visit 5**	**Visit 6**	**Visit 7 TC**	**Visit 8**	**Visit 9, 11, 13 etc. TC**	**Visit 10, 12, 14 etc.**	**PTDV[c]**	**Study Closure Visit (SCV)[d]**
Assessment	Day −7 ± 7 d	Day 0	Day 7 ± 3 d	Day 30 ± 7 d	Day 90 ± 7 d	Day 180 ± 7 d	Day 270 ± 14 d	Day 360 ± 14 d	~15, 21, 27 etc. months[e] ± 14 d	~18, 24, 30 etc. months[e] ± 14 d	≤15 d after last dose	≤60 days after PACD[f]
Signed Informed Consent	√											
Eligibility criteria	√	√										
Medical and surgical history	√											
Demographics	√											
Vital signs (pulse, BP)	√	√									√	√
Weight and height	√											
Urine Pregnancy test[g]	√	√										
Local laboratory analyses[h]		√										
Electrocardiogram (ECG)		√										
Health Economic Assessment[i]		√				√		√		√	√	√
Dispense Study Medication		√			√	√		√		√		
Return Study Medication					√	√		√		√	√	√
Drug accountability					√	√		√		√	√	√
Compliance reminder			√	√	√	√	√	√	√	√		
Dietary and lifestyle advice[j]	√	√			√	√		√		√	√	
Concomitant medications[k]		√	√	√	√	√	√	√	√	√	√	√
AEs of interest and DAEs[l]			√	√	√	√	√	√	√	√	√	√
Potential endpoint events including bleeding events[l]			√	√	√	√	√	√	√	√	√	√
Serious Adverse Events[m]		√	√	√	√	√	√	√	√	√	√	√

a The enrolment and randomisation visits should *preferably* be separated by at least 7 days (**mandatory** for women of childbearing potential) but can be combined into one single visit given that the patient has had sufficient time to consider study information, and that all information necessary to assess eligibility is available
b TC = Telephone Contact
c The PTDV (Premature Treatment Discontinuation Visit) is conducted only for patients who prematurely and permanently stop study medication. PTDV patients should also perform SCV at the end of the study
d The SCV may be a telephone contact in exceptional cases
e 1 month = 30 calendar days
f PACD = Primary Analysis Censoring Date (see Section 12.2.4)
g Only applicable for women of childbearing potential (ie, those who are not chemically or surgically sterilised or post-menopause)
h For laboratory assessment details, see Section 6.4.6
i To collect health care utilisation associated with hospitalisations and utilities assessed by Euro Quality of Life-5 dimensions (EQ-5D) to support health technology assessment and health economic modelling
j According to local treatment guidelines
k Detailed recording of **all** concomitant medication at randomisation (baseline) and at the study closure visit. In between, detailed recording of concomitant medication only includes of ASA and ADP receptor antagonist use and any medication given in association with SAEs and potential endpoint events, from one month prior to start date of the event until one month post start date of the event.
l AEs of interest, endpoint events and DAEs will be collected from randomisation throughout the study until and including the SCV
m SAEs will be collected from the time of informed consent throughout the study until and including the SCV

3.2 Rationale for study design, doses and control groups

This is a randomised, double blind, placebo controlled parallel group event-driven study. The primary objective of the study is to compare the effect of long-term treatment with ticagrelor bd vs. placebo for the prevention of major CV events (composite of CV death, MI or stroke) in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke. 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 T2DM at high CV risk.

The ticagrelor dose (90 mg bd) is the dose that was evaluated in PLATO, the pivotal phase III efficacy and safety study in patients with ACS. The dose in PLATO was based on pharmaco-dynamics (PD), efficacy, and safety information gained from phase II studies, which demonstrated that the 90 mg dose was well tolerated and showed high and consistent levels of inhibition of platelet aggregation (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%, without an increase in major bleeding, although non-CABG major bleeding did show greater rates with ticagrelor compared to clopidogrel. Ticagrelor at 90 mg bd was associated with a positive benefit: risk profile in patients with ACS. The benefit: risk profile in a subgroup of patients with DM was consistent with the overall results of PLATO.

Available data do not support a higher ticagrelor dose, as the proposed 90 mg bd dose is expected to generate near maximal inhibition of platelet aggregation. Neither do available data support a lower dose, since a lower ticagrelor dose would result in a 2-3 times increase in variability in IPA and substantially lower mean trough IPA, similar to that achieved with clopidogrel.

A placebo controlled study on a background of low-dose ASA, unless contraindicated or not tolerated, has been chosen since low-dose ASA is standard therapy for prevention of atherothrombotic events in diabetic patients with coronary artery disease (Rydén et al 2013, Smith et al 2011).

To explore effects on quality of life, EQ-5D will be used. It has been extensively used within CV research to assess patient health related quality of life in trials of new treatments, and has showed both high validity and reliability (Brooks 1996).

In PEGASUS, both the 90 mg and 60 mg regimens of ticagrelor were superior to placebo in the prevention of thrombotic CV events (composite endpoint: CV death, MI and stroke) with a consistent treatment effect over the entire study period, yielding a 15% RRR for 90 mg and 16% RRR for 60 mg. Although the efficacy profiles of ticagrelor 90 mg and 60 mg were similar to each other, there is evidence that the lower dose has a better tolerability and safety profile in relation to dyspnoea and risk of bleeding, and leads to fewer discontinuations from

study drug. No patient subgroups were identified as having a different efficacy and safety profile to that of the overall study population.

The critical endpoints selected for the benefit-risk assessment were all-cause mortality, MI, and stroke, which are considered against the risks of fatal bleeding and intracranial haemorrhage, all describing irreversible harm events. For the composite endpoints representing death or irreversible harm, both ticagrelor doses clearly showed a positive benefit-risk balance, with more events of death or irreversible harm prevented than caused. For the ticagrelor 60 mg group, all-cause mortality, CV death, MI and stroke all contributed to the benefit. For the ticagrelor 90 mg group, CV death, MI and stroke all contributed to the benefit, while all-cause mortality was neutral.

In PEGASUS, the efficacy profiles of ticagrelor 90 mg and 60 mg administered with low-dose ASA, were similar to each other. The lower dose had a better tolerability profile with regard to dyspnoea, less risk of bleeding, and lead to fewer discontinuations from study drug. Patients with diabetes did not have a different efficacy and safety profile to that of the overall study population. Hence, in order to use the lowest effective dose and taking the overall benefit-risk into consideration the dose in THEMIS will be ticagrelor 60 mg bd.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

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.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Men or women ≥50 years of age

3. Diagnosed with T2DM defined by ongoing glucose lowering drug treatment prescribed by a physician for treatment of T2DM since at least 6 months prior to Visit 1

4. At high risk of CV events, defined as history of percutaneous coronary intervention or coronary artery bypass graft or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery.

4.2 Exclusion criteria

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

1. Previous MI*[*] (with the exception of definite secondary MI [eg, due to coronary revascularization procedure, profound hypotension, hypertensive emergency, tachycardia, or profound anaemia])

2. Previous stroke (transient ischaemic attack [TIA] is not included in the stroke definition)

3. Planned use of ADP receptor antagonists (eg, clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol. Planned use of ASA treatment at doses >150 mg od

4. Planned coronary, cerebrovascular, or peripheral arterial revascularization

5. Anticipated concomitant oral or intravenous therapy with strong cytochrome P450 3A4 (CYP3A4) inhibitors or CYP3A4 substrates with narrow therapeutic indices that cannot be stopped for the course of the study:

   - Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin (but not erythromycin or azithromycin), nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir
   - CYP3A4 substrates with narrow therapeutic index: quinidine, simvastatin at doses >40 mg daily or lovastatin at doses >40 mg daily

6. Need for chronic oral anticoagulant therapy or chronic low-molecular-weight heparin (at venous thrombosis treatment not prophylaxis doses)

7. Patients with known bleeding diathesis or coagulation disorder, or with uncontrolled hypertension (defined as a systolic BP ≥180 mmHg and/or diastolic BP ≥100 mmHg)

8. History of previous intracerebral bleed at any time, gastrointestinal (GI) bleed within the past 6 months prior to randomisation, or major surgery within 30 days prior to randomisation

9. Increased risk of bradycardic events (eg, known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia) unless treated with a pacemaker

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

11. Renal failure requiring dialysis

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* Previous MI herein refers to a documented hospitalisation with a final diagnosis of spontaneous MI

12. Women 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 women who have a positive pregnancy test at enrolment or randomisation OR women who are breast-feeding

13. Inability of the patient to understand and/or comply with study procedures and/or follow up, in the opinion of the investigator, OR any conditions that, in the opinion of the investigator, may render the patient unable to complete the study

14. Any condition which in the opinion of the investigator would make it unsafe or unsuitable for the patient to participate in this study (eg, long-term concomitant treatment with non-steroidal anti-inflammatory drugs [NSAIDs]), or any condition outside the atherothrombotic study area with a life expectancy of less than 2 years based on investigator's judgement

15. Participation in another clinical study with an investigational product within 28 days prior to enrolment or previous randomisation to an investigational product in another ongoing clinical study. Participation in any previous study with ticagrelor. Previous randomisation in the present study

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

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Patients should be fasting (at least 6 hours) before blood sampling for baseline laboratory analysis.

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

Restrictions regarding concomitant medications are described in Section 5.6.

5.2 Patient enrolment and randomisation

The Principal Investigator or delegate 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) potential patients a unique enrolment number, beginning with 'E#'

4. Assign enrolled patient a unique randomisation code (patient number) in IVRS/IWRS.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Patients can only be randomised into the study once.

5.2.1 Procedures for randomisation

The randomisation codes will be computer generated by AstraZeneca R&D using the AZ Global Randomisation system (GRand) and loaded into the IVRS/IWRS database. Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two treatment arms. Randomisation will be done via IVRS/IWRS at Visit 2. The IVRS/IWRS will allocate randomisation codes sequentially within each centre as patients become eligible for randomisation. Once a block of randomisation codes is exhausted, the next available block will be allocated by the IVRS/IWRS to the centre. For each patient randomised the IVRS/IWRS will provide the investigator with a unique Kit ID number matching the treatment arm assigned to the patient. Following randomisation, the first dose of study medication will be administered to the patient as soon as possible.

At randomisation and every subsequent dispensing visit the patient should always be provided medication with the Kit ID(s) allocated by the IVRS/IWRS. If a patient receives the incorrect randomised treatment at any time during the study, this must be corrected as soon as discovered.

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.

The following steps should be taken in the event that a patient, who does not meet inclusion/exclusion criteria, is found to have been inadvertently randomised in an AstraZeneca study:

(a) The investigator or monitor should inform the AstraZeneca study team physician immediately. Ensuring patient safety must always be the number one priority

(b) Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. After a discussion between the study team physician and investigator, a decision may be reached that the patient should discontinue study medication. The rationale for discontinuing study medication must be clearly documented. The patient should remain in the study for follow up in accordance with defined study procedures including follow-up on endpoints through the end of the study consistent with the ITT principle

(c) In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow up in accordance with defined study procedures.

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. Ticagrelor tablets and matching ticagrelor placebo tablets will be provided (see Section 5.5.1), identical in appearance and with the same number, size, and packaging of tablets. Each pack will be labelled with a unique pack ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator.

No member of the extended study team at AstraZeneca, the EC, International Steering Committee, or the CEC, personnel at investigational centres or any CRO handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the Supply Chain Study Management department, and the Patient Safety department at AstraZeneca.

A 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 (see Section 12.4.2). The DMC will review safety data on a periodic basis, including the incidence of AEs, and conduct safety assessments to ensure the ongoing safety of study patients. The DMC responsibilities, authorities, and procedures will be documented in a DMC charter. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment allocation for each randomised patient, will be available to the investigator(s) or pharmacists 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 treatment. The AstraZeneca physician or delegate should be consulted whenever possible prior to the investigator breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff. The number of individuals at the study site who become aware of the treatment status should be kept to an 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 drug and that potentially require expedited reporting to regulatory authorities. 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 90 mg placebo	Plain, round, yellow, film-coated tablet, containing zero active therapy (identical in appearance to active)	AstraZeneca
Ticagrelor 60 mg	Plain, round, white, film-coated tablet, 60 mg	AstraZeneca
Ticagrelor 60 mg placebo	Plain, round, white, film-coated tablet, containing zero active therapy (identical in appearance to active)	AstraZeneca

5.5.2 Doses and treatment regimens

At the randomisation visit eligible patients will be randomly assigned to 1 of 2 treatments (see Table 2):

- Ticagrelor 60 mg, one tablet bd given orally
- Ticagrelor 60 mg placebo, one tablet bd given orally

Until the new ticagrelor 60 mg bd study medication with matching placebo is available at the individual study site, ticagrelor 90 mg, one tablet bd given orally, or corresponding placebo, will be used.

Randomisation and treatment pack assignment will be managed via the IVRS/IWRS and the first dose of study medication should be taken as soon as possible after randomisation. Subsequent maintenance doses should be taken morning and evening, at approximately 12-hour intervals, during 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.

5.5.2.1 Dose Switch strategy

When the new study medication comprising of ticagrelor 60 mg or corresponding placebo is locally available at study site, patients already randomized to ticagrelor 90 mg or corresponding placebo will be switched to the new study medication at the next planned visit.

The dose switch must occur on an on-site visit. If the next planned visit is a scheduled telephone contact (e.g. Visit 3, 4, 7, 9, 11, 13 etc.), the patient must be re-scheduled to come in for an on-site visit. By following this strategy all patients at a study site that currently are treated with ticagrelor 90 mg or corresponding placebo, will be switched to the new medication (ticagrelor 60 mg or corresponding placebo) within a 3 months period counted from when the new study medication is available at site.

At the discretion of the PI, an additional visit can be scheduled to allow for a dose switch ahead of next planned visit.

5.5.3 Development of indication for ADP receptor antagonist during study

If a patient randomised to study medication develops an indication for use of an ADP receptor antagonist according to medical guidelines (eg, an ACS or PCI), selection of the appropriate agent for individual patients is at the discretion of the investigator or treating physician and should be made in accordance with local medical guidelines and standard of care.

The patient must temporarily stop study medication during the open-label therapy with the ADP receptor antagonist. Patients should return to randomised treatment (ticagrelor or placebo) when there is no longer an indication for ADP receptor antagonist therapy according to medical guidelines.

5.5.4 Duration of treatment

The study is event-driven and 19000 randomised patients are estimated to be required in order to collect 1385 adjudicated primary endpoint events. The anticipated maximal duration of treatment with study medication for an individual patient is 58 months. However, the actual duration of the study will be based on accrual of the pre-determined number of adjudicated primary endpoint events, and therefore the final treatment time may be shorter or longer than 58 months. The expected minimum follow-up period is 29 months and the expected average follow-up period is 40 months, based on an enrolment period of 28 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 adjudicated primary endpoint events (1385).

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.

5.5.5 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.

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and in the original container. The study medication label and the IB specify appropriate storage.

5.6 Concomitant and post-study treatments

5.6.1 Recording of concomitant medication

Detailed recording of **all** concomitant medications (baseline recording) will be made **only** at the randomisation visit (visit 2) and at the study closure visit. Detailed recording of ASA and ADP receptor antagonist use will continue from randomisation throughout the study. In addition, concomitant medication will be recorded in association with SAEs and potential endpoint events from one month prior to start date of the event until one month post start date of the event.

5.6.2 Anti-diabetic treatment and risk factor management

All patients will receive dietary and life-style advice during the study (including recommendation on smoking cessation when applicable), in accordance with local diabetes treatment guidelines. Anti-diabetic medication and medications to treat concomitant risk factors (eg, dyslipidemia and hypertension) should be prescribed, aiming at target levels for glycemic control and risk factor management, according to guidelines.

5.6.3 Oral antiplatelet therapies

Patients requiring antiplatelet therapy other than low-dose ASA will be excluded at study entry.

5.6.3.1 Low Dose ASA (defined as 75 to 150 mg od)

In accordance with national and international clinical practice guidelines, all patients should take open label ASA at a dose of 75 – 150 mg once daily throughout the study, unless contraindicated or not tolerated. The patient will be responsible for the ASA supply throughout the study.

5.6.3.2 High Dose ASA (>150 mg od)

The concomitant use of ASA in any dose >150 mg od 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 dose of ASA >150 mg od is not permitted in combination with study medication.

5.6.3.3 ADP receptor antagonists

Planned concomitant treatment with any of other ADP receptor antagonists is not allowed in the study. Patients who develop an indication for treatment with an ADP-receptor antagonist during the study may be treated open-label at the discretion of the investigator, as described in Section 5.5.3. Blinded study medication must then be discontinued but should be resumed when open-label treatment with the ADP receptor antagonist is stopped.

5.6.3.4 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 ASA, is considered essential during the study, blinded study medication must be discontinued but should be resumed when open-label treatment with dipyridamole is stopped.

5.6.3.5 Approved PDE3 inhibitors for claudication (eg, cilostazol)

Planned concomitant treatment with any approved PDE3 inhibitor (ie, cilostazol) is not allowed during the study. If open label treatment with a PDE3 inhibitor, whether or not in combination with ASA, is considered essential during the study, blinded study medication must be discontinued but should be resumed when open-label treatment with the PDE3 inhibitor is stopped.

5.6.4 Parenteral antiplatelet therapies

5.6.4.1 GPIIb/IIIa receptor antagonists

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

5.6.5 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.

5.6.6 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.

5.6.7 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 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. When pain management is needed, acetaminophen/paracetamol is preferred.

5.6.9 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. Additional details can be found in the IB.

5.6.10 CYP450 interactions

5.6.10.1 CYP3A4 inhibitors

Strong inhibitors of CYP3A4 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.

5.6.10.2 CYP3A4 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 $\leq$ 40 mg daily or any approved 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 CYP3A4 also should be avoided (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, dexamethsaone) as plasma levels of ticagrelor could be reduced.

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.

5.6.11 Surgery

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

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

5.6.12 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 or treating physician. As with all other surgeries, investigators should collect and record all bleeding events occurring during the surgery or invasive procedurals. After the surgery or procedure, study medications should be restarted (if interrupted) as soon as possible.

Other medication, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator or treating physician.

5.7 Treatment compliance

The administration of study medication should be recorded in the eCRF. All stops of study medication prescribed by the investigator or treating physician should be recorded. In addition, any non-prescribed temporary stops (>1 week) of study medication should be recorded.

Missed doses of ticagrelor or placebo blinded study medication should not be compensated for (ie, if a dose is missed the next regularly scheduled dose should be taken and should not be doubled).

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 to and returned from the patient.

Patients will be asked to bring all unused study medication and empty packages to the investigational centre at each on-site visit. The investigator or delegate will enter the amount of returned tablets in the eCRF and make an assessment regarding patient treatment

compliance. Any patient found to be noncompliant would 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. 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 bleeding, see Section 5.6.11
- Major bleeding, see Section 6.4.5.2
- Need of treatment with prohibited concomitant medications, see Section 5.6.

For other surgery or other invasive procedures, study medication may be continued or interrupted temporarily at the discretion of the investigator, see Section 5.6.12.

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, including but not limited to these examples:
  - Incorrectly randomised patient in whom the inclusion/exclusion criteria violation would put the patient at undue risk
  - AE for which the investigator thinks continued treatment may put the patient at undue risk
  - Severe non-compliance to study protocol
  - Pregnancy.

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

5.8.3 Procedures for permanent discontinuation of a patient from study medication

Patients permanently discontinuing study medication should be given conventional therapy, if applicable, and should continue the regular visits (see Section 5.8.3.1).

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 AEs (if any). These data will be ascertained and documented by the investigator and recorded in the eCRF as appropriate. AEs 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. Discontinuation from study medication is not the same as complete withdrawal from the study (withdrawal of consent), which has a direct impact on the potential validity of all study data, and should be avoided wherever possible.

5.8.3.1 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 within 15 days after the study medication is stopped. The patient will continue attending subsequent study visits according to schedule (Table 1) until PACD is declared by the EC. The patient will then return for their SCV as soon as feasible but no later than 60 days after the PACD has been declared. It is essential that the patients attend the SCV in person whenever possible.

5.8.3.2 Patient refuses to continue in-person study visits but agrees to undergo modified follow-up

If the patient refuses to continue in-person study visits, but agrees to undergo modified follow up, the in-person PTDV visit should be done within 15 days after the study medication is stopped. 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) 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 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 decision must be documented (see Section 5.9). At the end of the

study, vital status on all such patients will be collected from publicly available sources, in accordance with local regulations.

5.8.3.4 Restart of study medication

Whenever possible, restart of randomised study medication should be encouraged, even if a PTDV was previously completed.

5.8.4 Study Closure Visit

All randomised patients should return for their SCV as soon as possible, but no later than 2 months (60 days), after the PACD is declared by the EC (see Section 12.2.4). The actual time-window will depend on eg the number of patients per site.

If a patient is unable to attend the SCV in person, telephone contact should be made to ascertain endpoint and AE information. At the SCV physicians caring for the patient will decide which medication the patient should receive as part of his/her ongoing clinical care.

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) addendum – Withdrawal of consent. The ICF addendum should be 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 AEs. 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.

N.B. 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.

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 SCV. The investigator or delegate will therefore attempt to collect information on all patients' vital status from publicly available sources at the SCV, in accordance with local regulations, even if informed consent has been withdrawn completely.

5.10 Study committees

5.10.1 Executive Committee (EC)

The EC will be responsible for the overall design, including the development of the protocol and any protocol amendments, supervision, interpretation and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The EC will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The EC will be comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under a separate charter.

To achieve an appropriate subgroup final distribution ratio, the Executive Committee will monitor particular subgroups and primary event rates and may cap enrolment to a particular subgroup based on the overall distribution and event rates. In particular, the enrolment of patients without ASA background treatment will be capped if it is considered inappropriately high or more than 5%.

5.10.2 International Steering Committee

The International Steering Committee is comprised of national lead investigators from each country where the study is conducted, and of relevant experts, and will be supervised by the EC. Members of the committee will be responsible for providing clinical guidance on study implementation and conduct in their respective country.

5.10.3 Clinical Endpoint Committee (CEC)

An independent CEC will be appointed and will adjudicate all potential endpoint events. The committee members will not have access to individual treatment codes for any patient or clinical efficacy and safety event. The precise responsibilities and procedures applicable for the CEC will be detailed in a separate CEC charter.

5.10.4 Data Monitoring Committee (DMC)

An independent DMC will be appointed and will report to the EC.

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 EC 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.

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 EC.

An interim analysis for efficacy will be performed by the DMC (see Section 12.2.3).

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave® Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The 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 the Rave® Web Based Data Capture (WBDC) system at the study site. 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 an AstraZeneca representative, the data will be frozen to prevent further editing. The Principal Investigator or a trained sub-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 site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment and randomisation procedures

Enrolment visit (Visit 1)

The following data will be collected in the eCRF at enrolment:

- Date of signed informed consent
- Eligibility criteria
- Demographics (including sex, date of birth, race, ethnic group)
- Relevant medical and surgical history
- Vital Signs (pulse and BP).

- Weight and height
- Urine pregnancy test (only applicable for women of childbearing potential).

Randomisation visit (Visit 2)

Patients that fulfil the eligibility criteria will undergo randomisation procedures. The following data will be collected in the eCRF:

- Eligibility criteria
- Vital Signs (pulse and BP)
- ECG (including recording of Heart Rate)
- Blood sampling for laboratory assessments (see Section 6.4.6)
- Urine pregnancy test (only applicable for women of childbearing potential)
- Dispensed study medication
- Concomitant medications (baseline recording, see Section 5.6.1)
- SAEs
- EQ-5D questionnaire (baseline for patients' health related quality of life, will be collected at clinic visits every 6th month in countries where an official language version is available).

6.2.2 Follow-up procedures

Dietary and lifestyle advice will be provided at each visit according to local diabetes treatment guidelines. The following assessments will be done at the follow-up visits:

Visit 3, 4, 7, 9, 11, 13 etc. (scheduled telephone contacts)

- AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs
- Concomitant medications (only ASA and ADP receptor antagonist use and concomitant medication in association with SAEs and potential endpoint events, see Section 5.6.1).

Visit 5 (on-site visit)

- Dispensed and returned study medication
- AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs

- Concomitant medications (only ASA and ADP receptor antagonist use and concomitant medication in association with SAEs and potential endpoint events, see Section 5.6.1).

Visit 6, 8, 10, 12, 14 etc. (on-site visits)

- EQ-5D questionnaire
- Dispensed and returned study medication
- AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs
- Concomitant medications (only ASA and ADP receptor antagonist use and concomitant medication in association with SAEs and potential endpoint events, see Section 5.6.1).

Dose Switch

- For procedures describing the dose switch please refer to section 5.5.2

Premature Treatment Discontinuation Visit (PTDV)

- Vital signs (pulse and BP)
- EQ-5D questionnaire
- Return of study medication
- AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs
- Concomitant medications (only ASA and ADP receptor antagonist use and concomitant medication in association with SAEs and potential endpoint events, see Section 5.6.1).

Study Closure Visit

- Vital signs (pulse and BP)
- EQ-5D questionnaire
- Return of study medication (not applicable for patients who have previously attended a PTDV)
- AEs of interest, SAEs, potential endpoint events including bleeding events (unexpected or of unanticipated quantity) and DAEs

- Detailed recording of all concomitant medications and concomitant medication in association with SAEs and potential endpoint events, see Section 5.6.1.

6.3 Efficacy

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 potential endpoint event, the investigator will complete information specific to that type of endpoint in the eCRF and compile relevant additional source information into an 'Endpoint Package', as described in the Event Reporting Manual for Investigators. The Endpoint Package will be sent to the CEC for central adjudication. The investigator should use the following definitions in assessing potential endpoint events. Additional details about the evaluations of potential endpoint events will be contained in the CEC charter.

6.3.1 Classification of Death

For the purpose of the efficacy analysis, deaths will be sub-classified by CV and non-CV primary cause. CV death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to a cerebrovascular event, death due to other CV causes (eg, pulmonary embolism, aortic disease, CV intervention), and deaths for which there was no clearly documented non-CV cause (presumed CV death).

Additionally, deaths will be sub-classified by coronary heart diseases death (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 CV Causes that are secondary to a coronary revascularization procedure.

6.3.2 Universal classification of Myocardial Infarction (MI)

The independent CEC will use the Third Universal MI definition (Thygesen et al 2012) as study specific MI criteria during adjudication. Additional details about the evaluations of potential MI events will be contained in the CEC charter.

6.3.3 Definition of Stroke

Stroke is defined as an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause. Stroke should be documented by imaging (eg, CT scan or magnetic resonance imaging [MRI] scan). Evidence obtained from autopsy can also confirm the diagnosis. Stroke will be sub classified, when possible, as either:

Primary ischaemic stroke
Primary ischaemic stroke is defined as an acute episode of focal brain, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue and documented by imaging. A primary ischemic stroke may also undergo hemorrhagic transformation (ie, no evidence of haemorrhage on an initial imaging study, but appearance on a subsequent scan).

Primary haemorrhagic stroke
Primary haemorrhagic stroke is defined as an acute episode of focal or global brain, spinal, or retinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid haemorrhage as documented by neuroimaging or autopsy. Microhaemorrhages (<10 mm) evident only on MRI are not considered to be a hemorrhagic stroke. Subdural and epidural bleeding will be considered intracranial haemorrhage, but not strokes.

Unclassified stroke
Stroke with unknown aetiology will be classified as unclassified stroke if the type of stroke could not be determined by imaging or other means.

Additional details about the evaluations of potential stroke events will be contained in the CEC charter.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An adverse event (AE) 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, electrocardiogram). 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.

6.4.1.1 Adverse Events of interest

Secondary objectives will include an assessment of the long-term effects of ticagrelor on the following AEs of interest:

- Dyspnoea
- Renal impairment
- Bradyarrhythmia
- Gout
- Pneumonia.

Any other non-serious AE unless discontinuation of study medication due to AE (DAE) will not be collected in the study.

6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) 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 Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs of interest (see Section 6.4.1.1) and DAEs will be collected from randomisation throughout the study until and including the SCV.

SAEs will be recorded from the time of informed consent throughout the study until and including the SCV.

Follow-up of unresolved adverse events

Any 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 electronic case report form (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 collect for each non-serious AE of interest and DAEs:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity

- Whether the AE is serious or not
- 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 for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- 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.

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, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The following definitions for intensity rating are:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)

3. 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?".

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 Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs of interest (see Section 6.4.1.1) spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'* or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) 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

Laboratory safety assessments will not be routinely done (except at baseline), but may be performed during the study at the investigators discretion. In association with an AE of interest, DAEs, SAE or potential endpoint event, different assessments may have to be undertaken, which could include local laboratory assessments, and which will be collected in the eCRF as appropriate.

The results from protocol-mandated vital signs are to 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 as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study medication.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE 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 vs. increasing creatinine). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs and SAEs.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study medication, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **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 AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the investigator(s) or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel should report the SAE to the appropriate AstraZeneca representative by telephone, recognizing that the same reporting timeframe (24 hours) still apply. The AstraZeneca representative will advice the investigators how to proceed.

If the initial or subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigator as soon as the system becomes available again.

6.4.4.1 Reporting of serious adverse events considered to be potential endpoint events

If a potential endpoint event meets the SAE criteria it must be reported in the eCRF by the investigator within the regular SAE reporting timelines (see Section 6.4.4).

All events involving non-fatal MI, non-fatal stroke, all-cause death or bleeding events will be defined as ‘potential endpoint events’. Once one of these potential endpoint event has been identified, the investigator will record this in the respective appropriate modules of the eCRF and report it to the CEC for central adjudication (see Section 12.4.1). Events of unstable angina pectoris and TIA that are judged by investigators to fulfil SAE criteria will be sent for adjudication to ensure that they are not MI or stroke.

The following events adjudicated to endpoints in the study, although qualifying as SAEs, will only be reported as primary endpoint events in the Clinical Study Report (CSR):

- Non-fatal MI

- Primary Ischaemic Stroke
- CV Death.

These adjudicated endpoint events will not be reported to health authorities as SAEs as they are considered part of the natural history of the condition under investigation and will be monitored by the independent DMC throughout the study. This approach aims to avoid unnecessary unblinding of treatment in patients with endpoint events that are also SAEs.

If it is determined by the CEC that a potential endpoint event does not meet the endpoint criteria, but is judged by investigators to fulfil SAE criteria, the event will be captured as an SAE and reported to the health authorities.

6.4.5 Bleeding assessments

Bleeding events that are self-limited, and do not prompt medical evaluation or intervention, need not to be reported. For all bleeding events that are unexpected or of unanticipated quantity, the investigator will complete information in the eCRF specific to that bleeding event. In addition, for all reported bleeding events relevant information will be compiled and sent to the CEC for central adjudication according to the following bleeding definitions: TIMI, PLATO (Wallentin et al 2009) and BARC (Mehran et al 2011). Additional details can be found in the CEC Charter.

Additionally, all bleeding events (including haemorrhagic stroke) fulfilling the SAE criteria will be reported as SAEs by the sponsor to the authorities. If the adjudication of a potential endpoint event unveils a bleeding event, eg, haemorrhagic stroke, not yet reported as SAE, it will be reported by AZ as SAE to the authorities.

6.4.5.1 Bleeding associated with procedures

Bleeding associated with procedures should **only** be reported as a bleeding event and AE/SAE if the bleeding exceeds what can be expected for the 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). Study medication may be resumed when the risk of bleeding is deemed low in the judgment of the investigator. 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 transfusions. It should be noted that platelet transfusion is unlikely to reverse bleeding in a patient receiving ticagrelor, as the new platelets are likely to be inhibited by ticagrelor as long as it is circulating in the blood.

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

6.4.6 Laboratory safety assessment

A urine pregnancy test (U-HCG) will be taken at visit 1 and repeated at visit 2 in women of childbearing potential.

The following baseline laboratory variables will be analyzed at local laboratories for all patients, preferably after 6 hours of fasting, and must have been collected between 30 days prior of randomization and at the latest on the day of the randomization, before first intake of study medication:

Clinical Chemistry (Serum or Plasma)	**Haematology (Whole blood)**
S/P-Creatinine	B-Haemoglobin
S/P-LDL-C	B-Platelet count
S/P-Triglycerides	B-Haemoglobin A1c

Urinanalysis

U-HCG (pregnancy test, only applicable for women of childbearing 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 SAEs or potential endpoint events, 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 Collection of specific information for liver related SAEs or DAEs

In patients with liver related SAEs or DAEs as judged by the investigator, in addition to the completion of the appropriate SAE/DAE eCRF, specific information should also be reported using the eCRF liver modules unless drug induced liver injury reasonably excluded (eg gallstone disease, liver tumours).

6.4.7 Electrocardiogram (ECG)

A 12-lead ECG (standard ECG with a paper speed of 25-50 mm/second covering at least 6 sequential beats) will be recorded at baseline (visit 2) after the patient has been lying down to rest for at least 5 minutes. Heart rate will be reported in the eCRF. The baseline ECG should be made available to the CEC upon request, to facilitate adjudication of potential cardiac ischaemic events.

6.4.8 Vital signs

Pulse and systolic and diastolic BP will be assessed using non-invasive equipment after the patient has been at rest for 5 minutes. Results will be recorded in the eCRF.

6.5 Patient reported outcomes (PRO)

Patients' health related quality of life will be measured using the EQ-5D quality of life questionnaire, see Section 6.9.1.

6.6 Pharmacokinetics (Not Applicable)

6.7 Pharmacodynamics (Not Applicable)

6.8 Pharmacogenetics (Not Applicable)

6.9 Health economics

Patients' health related quality of life will be measured using EQ-5D quality of life questionnaire (see Section 6.9.1). The EQ-5D-5L version of the questionnaire will be used.

6.9.1 Health economic assessment (EQ-5D)

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 5 dimensions are mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.

For each dimension of the EQ-5D-5L questionnaire responders are asked to state their status on a five level (5L=5 levels) ordinal scale; whether they experience no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), or extreme problems (level 5).

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, Dyer et al 2010) 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 site staff. The site staff will transfer the responses into the eCRF. All patients will be asked to complete the EQ-5D questionnaire every 6 months at on-site visits from Visits 2 throughout the study until SCV. The EQ-5D will only be administered in countries where an official language version is available.

6.9.2 Health care resource utilisation

Information on health care resource utilisation associated with hospitalisation admissions and health related quality of life is to be collected until SCV to enable health technology assessment, health economic analysis and health economic modelling. Resource utilisation

and health related quality of life are to be recorded in the eCRF beginning at randomisation. The following types of resources will be recorded for all hospitalisations:

- Admission date
- Discharge date
- Discharge destination
- Ward type information including duration of stay, for example:
  - General
  - CCU (Coronary Care unit)
  - ICU (Intensive Care Unit)
- Final discharge diagnosis
- Major secondary discharge diagnosis (if present)
- Main procedures.

The variables collected to support health economic evaluation are the EQ-5D questionnaire at randomisation and every 6 months thereafter at on-site visits, and information on all hospitalizations during the course of the study.

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, thus requiring additional sample volumes.

Table 3 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
	Clinical chemistry	**5**	**1**	**5**
	Haematology	**3**	**1**	**3**
Total				**8 mL**

7.2 Handling, storage and destruction of biological samples

The baseline laboratory samples (see Section 6.4.6) and any additional laboratory safety samples taken at the investigators discretion or connected to an endpoint event will be analysed locally. The safety samples will be disposed after analyses.

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 ICH/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.2 Subject data protection

The Informed Consent Form 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/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 patient. The investigator/Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee/IRB, and to the study site staff.

The opinion of the Ethics Committee should be received in writing. The investigator should submit a notification of direction/determination as well as a copy of the IRB written approval to AstraZeneca before enrolment of any patient into the study.

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

AstraZeneca 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 Ethics Committee 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 will provide Regulatory Authorities, Ethics Committees/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 Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study medication. AstraZeneca 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) or delegate 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
- Ensure each patient is notified that they are free to discontinue from the study at any time
- 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 study specific procedure
- 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 EC 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 Clinical Study Protocol).

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

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

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee 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 Ethics Committee.

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 source data verification. 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, GCP, guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca 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 is necessary for a representative of AstraZeneca to visit the investigational study site 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 between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol 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 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).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, 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 and that study drug accountability checks are being performed
- Perform source data verification (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)

The AstraZeneca representative will be available between visits if the investigator(s) or other study site personnel need information and advice about the study conduct.

9.3.1 Source data

The Clinical Study Agreement (CSA) will specify the location of source data.

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

9.4 Study agreements

The Principal Investigator at each 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 Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol 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 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 Q1 2014 and to end by Q4 2018.

Planned average treatment duration in the study: 40 months.

AstraZeneca will notify investigators 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 EC 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 BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre staff.

Data will be entered in the WBDC system at the study site. Trained site staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. The eCRF instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed/queried and updated as needed. The Principal Investigator is responsible for signing the eCRF and this can be delegated to a trained sub-investigator. The eCRF is signed electronically as per the eCRF instructions. The data will be validated as defined in the Data Management Plan. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

The patients will fill in PRO (EQ-5D) paper form under the supervision of the site staff. The site staff will transfer the responses into the eCRF.

Dictionary coding

Medical coding is done using the most current version of MedDRA (Medical Dictionary for Regulatory Activities) and AstraZeneca Drug Dictionary.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data. The Data Management Centre determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (IVRS/IWRS, etc) will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variables (Not Applicable)

11.2 Calculation or derivation of safety variable(s) (Not Applicable)

11.3 Calculation or derivation of patient reported outcome variables

See Section 12.2.1.3.

11.4 Calculation or derivation of pharmacokinetic variables (Not Applicable)

11.5 Calculation or derivation of pharmacodynamic variables (Not Applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not Applicable)

11.7 Calculation or derivation of health economic variables

See Section 12.2.1.3.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Full analysis set

All patients who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed 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 death). All efficacy variables will be analysed using the FAS.

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomised ticagrelor or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to ticagrelor but actually given placebo) will be accounted for in the actual treatment group. A patient who in error has received both ticagrelor and placebo will be accounted for in the randomised treatment group.

12.2 Methods of statistical analyses

This section provides a summary of the planned statistical analyses. Further details will be provided in a Statistical Analysis Plan.

12.2.1 Efficacy analysis

All efficacy analyses will be based on the ITT principle using the FAS, including only adjudicated endpoint events. Investigators are instructed to report all potential endpoint events in the eCRF, even those that may not meet strict endpoint definitions, to ensure all potential events are reviewed and adjudicated by the CEC.

For time to event variables, treatments will be compared using a Cox proportional hazards model with a factor for treatment group, using the Efron method for ties. Censoring principles are described in Section 12.2.4. The p-value (calculated using the Wald test), hazard ratio (HR) and 95% confidence interval will be reported. Kaplan-Meier estimates of the cumulative risk will also be presented.

The family wise error rate will be controlled for the primary and secondary efficacy analyses by applying a hierarchical test sequence as described in Section 12.2.1.2. No other adjustments for multiple comparisons will be made.

As supportive analyses, data from patients with diabetes in PEGASUS (patients with MI within 1-3 years) and EUCLID (PAD patients) will be pooled and analyzed with and without

data from this study. These analyses will be described in a separate SAP and reported separately.

12.2.1.1 Primary efficacy variable

The primary efficacy variable, time from randomisation to the first occurrence of any event from the composite of CV death, MI or stroke, will be analysed using the methodology described in Section 12.2.1. The null hypothesis of no treatment effect,

H_0: HR (ticagrelor divided by placebo) = 1,

vs. the alternative hypothesis,

H_1: HR $\neq$ 1,

will be tested at 4.96% two-sided significance level.

The assumption of proportional hazards 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.

To assess possible effects of missing data, sensitivity analyses will be done as follows. The event rate in the placebo arm will be used to estimate the intensity of a Poisson process. Based on the missing follow-up time, i.e. the time from censoring to PACD, the expected number of events in the ticagrelor group that could have been observed if the patients had completed the study will be estimated from the Poisson process. The comparison of ticagrelor and placebo will be recalculated with these additional events. If the result is still significant with these additional events, the intensity of the Poisson process will be increased and events will be added to the ticagrelor group until the primary analysis is non-significant.

Subgroup analyses on the primary efficacy variable will be performed to evaluate variation of treatment effect. Relevant subgroups, eg age, sex, race, ASA use and medical history, will be examined. Hazard ratios and 95% confidence intervals will be reported for each subgroup as well as p-values for the tests of interaction between treatment and each subgroup.

12.2.1.2 Secondary efficacy variables

The secondary efficacy variables will be analysed using the methodology described in Section 12.2.1.

- 1. Time from randomisation to death of CV cause
- 2. Time from randomisation to first occurrence of MI
- 3. Time from randomisation to first occurrence of ischaemic stroke
- 4. Time from randomisation to death of any cause.

Endpoints 1-4 will be included in the confirmatory testing procedure. Only if the treatment effect on the primary efficacy variable is significant at the 4.98% level, will the secondary efficacy variables be tested in a confirmatory sense in the order given above. The hypothesis testing will continue at the 4.98% significance level until the first statistically non-significant treatment difference ($p \geq 0.0498$) is observed.

12.2.1.3 Exploratory variables

Other objectives are exploratory, with the purpose of comparing other long-term treatment effects of ticagrelor vs. placebo.

Time to event variables will be analysed using the methodology described in Section 12.2.1:

- Time from randomisation to first occurrence of any event from the composite of all- cause death, MI or stroke
- Time from randomisation to first occurrence of stroke
- Time from randomisation to first occurrence of any event from the composite of all- cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding (irreversible harm events).

Descriptive reporting of the resource utilisation data and health related quality of life data based on the EQ-5D are to be documented 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.

12.2.2 Safety variables

All analyses of safety variables will be based on the safety analysis set as described in Section 12.1.2.

12.2.2.1 Bleeding events

Analysis of time from randomisation to each of the following endpoints will be performed using the methodology described in Section 12.2.1:

- Time to first TIMI Major bleeding event
- 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 bleeding event.

The assessment of time to bleeding events will focus on the items above but will also include analysis of time to first adjudicated event for additional categories of bleeding according to

the TIMI, PLATO and BARC definitions. Exploration of potential risk factors for bleeding events will be performed. 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.

12.2.2.2 SAEs and AE of interest

AEs of interest, DAEs as well as SAEs will be evaluated. Summaries, by system organ class and preferred term using MedDRA, will be presented by treatment group using descriptive statistics.

12.2.3 Interim analysis for efficacy

An interim analysis will be performed by the DMC. The interim analysis will be performed following the accrual and confirmation by adjudication of 517 primary events . The stopping boundary at the interim analysis is a 2-sided p-value <0.001 for both the primary endpoint (CV death, MI, or stroke) and for the CV death endpoint (the 1st secondary efficacy endpoint). The interim p-value is small enough for the final analysis to be conducted at a significance level of 4.96%, with the family wise error rate controlled at 5.00%. These boundaries were determined using a Haybittle-Peto procedure (Haybittle 1971, Peto et al 1976).

If a recommendation to stop the study is made at the interim, all subsequent testing will be done at the same significance level as for the interim.

12.2.4 Censoring

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

The PACD 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 PACD but before the SCV will also be collected and adjudicated. These events will 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 PACD 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 (3) the date of death from non-cardiovascular causes. For endpoints not including death, all deaths are censoring events. In safety time-to-event analysis of bleeding, patients not having suffered any bleeding event in the given category will be censored at the earlier of SCV, 7 days after last dose of study drug, death, last contact or withdrawal of consent.

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, in the main analyses patients will be censored at the time of consent withdrawal. However, the determination of all-cause death 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 death as a single endpoint, in sensitivity analysis 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 or stroke has been estimated to be 2.5% annually in a population consisting of patients with T2DM at high risk of CV events without medical history of previous MI or stroke.

The final primary treatment comparison will be made at a significance level of 4.96% adjusted for the planned efficacy interim analysis. Assuming a true hazard ratio of 0.84 between ticagrelor and placebo, 1385 primary endpoint events will provide a power of 90%.

With an annual event rate of 2.5% in the placebo treatment group, 19000 patients, randomised in a 1:1 ratio, with an average follow-up period of 40 months, are estimated to provide the required number of primary events. The expected minimum follow-up period is 29 months, based on an enrolment period of 28 months.

The expected number of patients who will be lost-to-follow-up is negligible and hence not considered in the determination of samples size.

12.4 Independent Data monitoring committees

12.4.1 Clinical Endpoint Committee (CEC)

See Section 5.10.3.

12.4.2 Data Monitoring Committee (DMC)

See Section 5.10.4.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca 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**

In the case of a medical emergency the investigator may contact the Study Team Physician at AstraZeneca R&D Mölndal.

Name	Role in the study	Address & telephone number
[redacted]	Lead Study Team Physician responsible for the protocol at AstraZeneca R&D Mölndal	[redacted]
[redacted]	Global Clinical Lead responsible for the protocol at AstraZeneca R&D Mölndal	[redacted]
[redacted]	Study Team Leader	[redacted]

13.2 Overdose

An overdose of study medication is defined as intake of more than 360 mg ticagrelor/ticagrelor placebo per 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 (eg, compression), and decompression or drainage may be required depending on the localisation, 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. The IB documents other symptoms that can be expected after an overdose of ticagrelor..

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **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 site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Pregnant women have not been included in any studies with ticagrelor.

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

Pregnancy itself is not regarded as an AE 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 site personnel inform appropriate AstraZeneca representatives immediately, or **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 site 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.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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 study site personnel should inform appropriate AstraZeneca representatives within 1 day as described in the maternal exposure Section 13.3.1.

The Informed Consent Form for Pregnant Partners should be completed in order to collect additional information regarding outcome of pregnancy.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Ticagrelor
Study Code	D513BC00001
Edition Number	1
Date	25 October 2013

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.

Clinical Study Protocol Appendix C	
Drug Substance	Ticagrelor
Study Code	D513BC00001
Edition Number	2
Date	19 June 2014

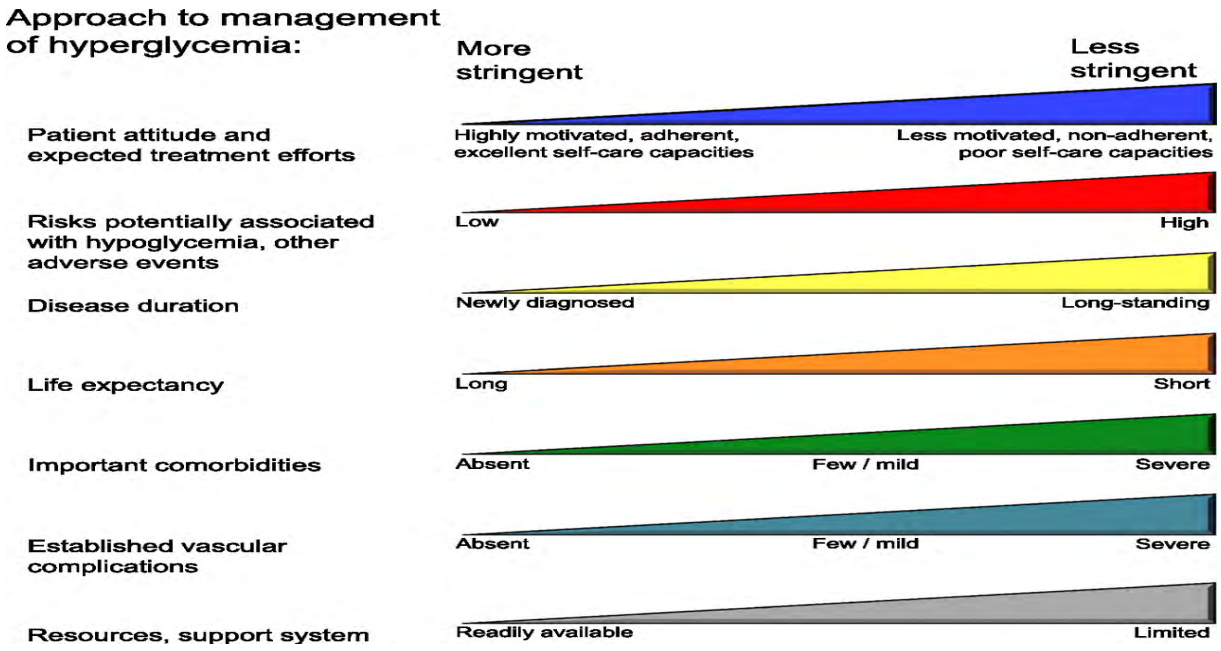
Appendix C
ADA/EASD Treatment Algorithm for Antihyperglycemic Therapy in Type 2 Diabetes Mellitus

1. ADA/EASD TREATMENT ALGORITHM FOR ANTIHYPERGLYCEMIC THERAPY IN TYPE 2 DIABETES MELLITUS

This appendix contains an excerpt from Inzucchi et al 2012, "Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)"

Full text available at doi: 10.2337/dc12-0413. Diabetes Care June 2012 vol. 35 no. 6 1364-79.

Figure 1 Depiction of the elements of decision making used to determine appropriate efforts to achieve glycemic targets



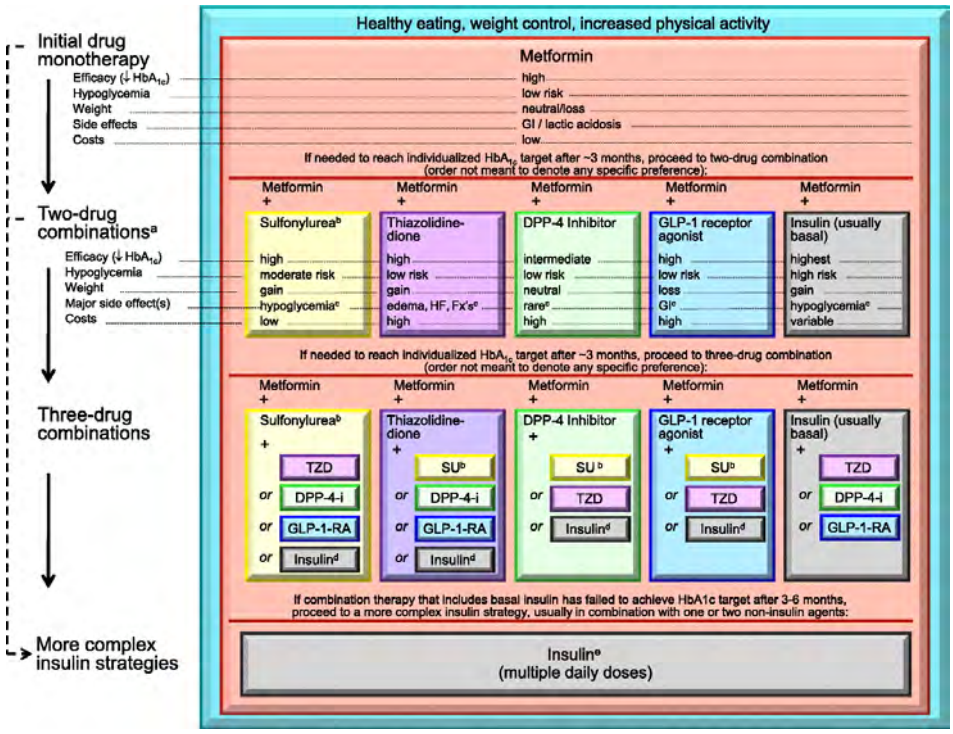
Inzucchi S E et al. Dia Care 2012;35:1364-1379

American Diabetes Association.

Depiction of the elements of decision-making used to determine appropriate efforts to achieve glycemic targets. Greater concerns about a particular domain are represented by increasing height of the ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA1c, whereas those toward the right are compatible with less stringent efforts. Where possible, such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied

rigidly but to be used as a broad construct to help guide clinical decisions. Adapted with permission from Ismail-Beigi et al. (20).

Figure 2 Antihyperglycemic therapy in type 2 diabetes: general recommendations

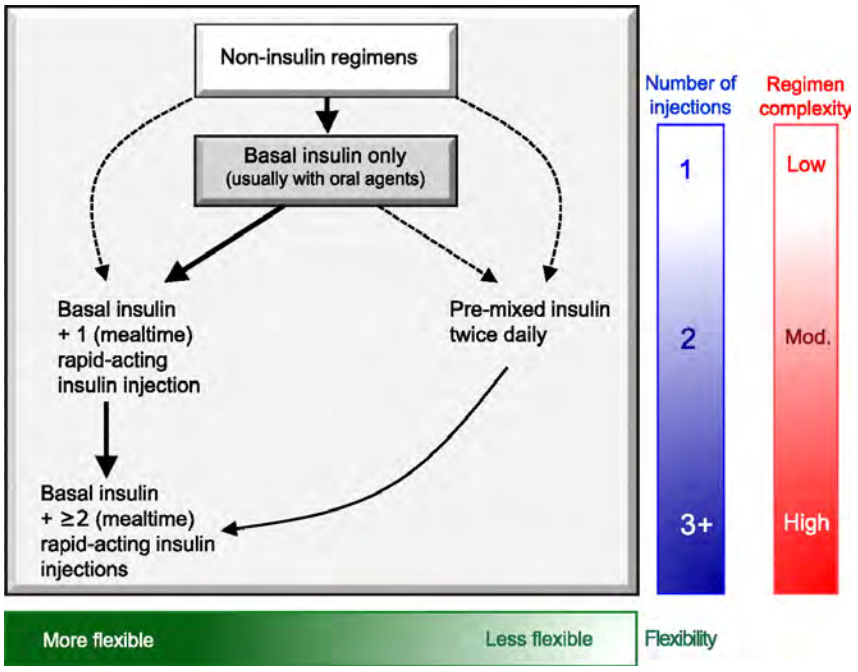


Inzucchi S E et al. Dia Care 2012;35:1364-1379

Moving from the top to the bottom of Figure 2, general recommendations of potential sequences of antihyperglycemic therapy is given. In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA1c target is not achieved after ~3 months, consider one of the five treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin (the order in the chart is determined by historical introduction and route of administration and is not meant to denote any specific preference). Choice is based on patient and drug characteristics, with the over-riding goal of improving glycemic control while minimizing side effects. Shared decision making with the patient may help in the selection of therapeutic options. The figure displays drugs commonly used both in the U.S. and/or Europe. Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. Other drugs not shown (α-glucosidase inhibitors, colesevelam, dopamine agonists, pramlintide) may be used where available in selected patients but have modest efficacy and/or limiting side effects. In patients intolerant of, or with contraindications for, metformin, select initial drug from other classes depicted and proceed accordingly. In this

circumstance, while published trials are generally lacking, it is reasonable to consider three-drug combinations other than metformin. Insulin is likely to be more effective than most other agents as a third-line therapy, especially when HbA1c is very high (e.g., ≥9.0%). The therapeutic regimen should include some basal insulin before moving to more complex insulin strategies (Figure 3). Dashed arrow line on the left-hand side of the figure denotes the option of a more rapid progression from a two-drug combination directly to multiple daily insulin doses, in those patients with severe hyperglycemia (e.g., HbA1c ≥10.0–12.0%). DPP-4-i, DPP-4 inhibitor; Fx's, bone fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea. [a]Consider beginning at this stage in patients with very high HbA1c (e.g., ≥9%). [b]Consider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas. [c]See Table 1[1] for additional potential adverse effects and risks, under "Disadvantages". [d]Usually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents. [e]Certain noninsulin agents may be continued with insulin (see text). Refer to Figure 3 for details on regimens. Consider beginning at this stage if patient presents with severe hyperglycemia (≥16.7–19.4 mmol/L [≥300–350 mg/dL]; HbA1c ≥10.0–12.0%) with or without catabolic features (weight loss, ketosis, etc.).

Figure 3 Sequential insulin strategies in type 2 diabetes



Inzucchi S E et al. Dia Care 2012;35:1364-1379

[1] Table 1 available in full text at doi: 10.2337/dc12-0413. Diabetes Care June 2012 vol. 35 no. 6 1364-79.

Basal insulin alone is usually the optimal initial regimen, beginning at 0.1–0.2 units/kg body weight, depending on the degree of hyperglycemia. It is usually prescribed in conjunction with one to two noninsulin agents. In patients willing to take more than one injection and who have higher HbA1c levels (≥9.0%), twice daily (bd) premixed insulin or a more advanced basal plus mealtime insulin regimen could also be considered (curved dashed arrow lines). When basal insulin has been titrated to an acceptable fasting glucose but HbA1c remains above target, consider proceeding to basal plus mealtime insulin, consisting of one to three injections of rapid-acting analogs (see text for details). A less studied alternative—progression from basal insulin to twice-daily premixed insulin—could be also considered (straight dashed arrow line). If this is unsuccessful, move to basal and in addition mealtime insulin. Figure 3 describes the number of injections required at each stage, together with the relative complexity and flexibility. Once a strategy is initiated, titration of the insulin dose is important, with dose adjustments made based on the prevailing glucose levels as reported by the patient. Noninsulin agents may be continued; although insulin secretagogues (sulfonylureas, meglitinides) are typically stopped once more complex regimens beyond basal insulin are utilized. Comprehensive education regarding self-monitoring of blood glucose, diet, exercise, and the avoidance of, and response to, hypoglycemia are critical in any patient on insulin therapy.

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