Academic and Clinical Central Office for Research and Development

Study Protocol

Dual antiplatelet therapy to Inhibit coronary Atherosclerosis and MyOcardial injury in patients with Necrotic high-risk coronary plaque Disease

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL

DIAMOND

EudraCT number 2014-000952-26

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CT	Computer Tomography
CTA	Clinical Trial Authorisation
CTCA	Computer Tomography Coronary Angiography
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF	Case Report Form
DNA	Deoxyribose Nucleic Acid
eGRF	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Authority
NIMP	Non Investigational Medicinal Product
PET	Positron Emission Tomography
PLATO	PLATelet Inhibition and Patient Outcomes
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAR	Unexpected Adverse Reaction

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Pathogenesis of Coronary Artery Disease

Coronary plaque rupture of mildly stenotic coronary atherosclerosis is the commonest cause of acute coronary thrombosis and myocardial infarction [Davies, 2000]. This is the dominant type of plaque event causing an acute coronary syndrome, especially in men. It is closely linked to hypercholesterolaemia and has a dominant inflammatory phenotype. Classical histological features include a lipid-rich pool, thin fibrous cap, paucity of vascular smooth muscle cells and an intense inflammatory cell infiltrate [Davies, 2000].

Plaque rupture does not invariably lead to thrombotic occlusion of the coronary artery. Coronary plaque events are very common and the majority of such events do not cause coronary occlusion [Mann & Davies, 1999; Davies, 2000]. Here, plaque rupture and thrombosis is organised, remodelled and incorporated into the atherosclerotic plaque itself. Indeed, 80% of plaques that cause over 50% diameter stenosis have evidence of old healed plaque rupture with incorporation of thrombus into the atheroma [Mann & Davies, 1999]. This process contributes to the progression of coronary atherosclerosis and explains the first appearance, or step change in severity, of angina pectoris.

Coronary plaque events are often not isolated. Plaque rupture can occur throughout the body and is not confined to a single vascular bed. Moreover, in patients with acute coronary syndromes, it is common for multiple plaque events to occur simultaneously and beyond the culprit lesion itself. Post-mortem studies indicate that, on average, 2.4 coronary thrombotic events occur in each patient who presents with fatal coronary heart disease [Mann & Davies, 1999; Davies, 2000]. This suggests that systemic and generalised mechanisms and mediators play an important role in addition to local factors within the coronary artery wall.

In summary, coronary atherosclerosis is characterised by multiple and recurrent plaque rupture events that are often sub-clinical and cause step-wise growth of the plaque as it heals and remodels. Patients undergoing repeated plaque rupture events are likely to be at increased risk of myocardial infarction, especially if such an event coincides with a period of increased blood thrombogenicity. If these patients can be identified then there would be a clear rationale for using powerful anti-platelet agents, such as ticagrelor, to dampen down their thrombotic potential and the risk of adverse cardiovascular events.

1.1.2 Ticagrelor

Ticagrelor (AZD6140) is a reversible and direct-acting oral antagonist of the adenosine diphosphate $P2Y_{12}$ receptor. It provides faster, greater, and more consistent $P2Y_{12}$ inhibition than clopidogrel [Gurbel *et al*, 2009]. In the PLATelet inhibition and patient Outcomes (PLATO) trial of 18,624 patients presenting with an acute coronary syndrome, ticagrelor was superior to clopidogrel for the prevention of cardiovascular events and death [Wallentin *et al*, 2009]. It is unknown whether these anti-platelet and anti-thrombotic benefits extend to patients with coronary artery disease in the absence of an acute coronary syndrome.

1.1.3 Non-invasive Imaging of the Vulnerable Plaque

In the study of coronary artery disease, many researchers have searched for a non-invasive imaging biomarker of plaque vulnerability and rupture. For the first time, we have demonstrated that 18F-fluoride positron emission tomography can detect high-risk coronary plaque in patients with stable coronary artery disease [Joshi *et al*, 2013].

In the vasculature, 18F-fluoride acts as a marker of novel calcification activity [Dweck *et al*, 2012a; Dweck *et al*, 2013]. Similar to other conditions, calcification in coronary atheroma occurs as a healing response to intense necrotic inflammation, making 18F- fluoride a useful marker of high-risk atherosclerotic plaque. We have previously demonstrated increased uptake of this tracer in the coronary vasculature localizing to individual coronary lesions and identifying patients with increased cardiovascular risk factor profiles [Dweck *et al*, 2012b]. More recently

we have conducted a prospective study of 40 patients with myocardial infarction in whom 18F-fluoride localised to the culprit plaque (Figure 1) in over 90% of patients [Joshi *et al*, 2013]. This finding was confirmed in 12 patients with a recent stroke undergoing carotid endartectomy where 18F-fluoride uptake was observed at the site of plaque rupture in 100% of patients and this uptake correlated with increased calcification activity and areas of necrosis on histology. Finally we studied 40 patients with stable coronary artery disease. Increased uptake was observed in 45% of these patients and this again localized to individual coronary plaques (Figure 2). Interestingly these lesions were associated with multiple high-risk markers on radiofrequency and gray-scale intravascular ultrasound (necrotic core, positive remodeling and microcalcification). Importantly, plasma high-sensitivity troponin concentrations were much higher in patients with 18F-fluoride positive plaques compared with patients without evidence of uptake (7.89±9.34 *versus* 3.10±1.89 ng/L, P=0·047; Figure 3). The latter observation is of particular interest as it supports the hypothesis that 18F-fluoride is detecting subclinical plaque rupture in those with stable disease, similar to its mechanism of activity following myocardial infarction. Moreover plasma troponin concentrations measured by a high-sensitivity assay also predict an adverse outcome amongst patients with stable coronary artery disease [Omland *et al*, 2013] and provide a useful surrogate biomarker of therapeutic efficacy.

1.1.4 High-Sensitivity Cardiac Troponin I

Cardiac troponins are regulatory muscle proteins that are released into the circulation following acute myocardial injury. Assays that quantify cardiac isoforms of troponin have greater specificity and sensitivity for the diagnosis of myocardial infarction than traditional cardiac enzymes. Indeed, we have demonstrated that this improved precision can lead to improved outcomes in patients with suspected acute coronary syndromes [Mills *et al*, 2011; Mills *et al*, 2012].

Recent advances have led to greatly improved assay sensitivity permitting quantification of extremely low concentrations of troponin with excellent precision. High-sensitivity cardiac troponin assays have limits of detection 10- to 100-fold lower than contemporary assays and are able to detect troponin in the circulation of the majority of healthy persons. Indeed, we have recently demonstrated important sex-specific thresholds for cardiac troponin when assessing patients with suspected acute coronary syndromes [Shah *et al*, 2013]. However, it is becoming increasingly recognized that plasma high-sensitivity troponin concentrations are powerful markers of future risk even when within the normal reference range. As previously indicated, plasma high-sensitivity troponin concentrations are increased in patients with high-risk 18F-fluoride positive coronary artery plaque [Joshi *et al*, 2013] and appear to predict an adverse outcome amongst patients with stable coronary artery disease [Omland *et al*, 2013].

1.2 RESEARCH HYPOTHESIS

Ticagrelor will reduce biomarkers of myocardial injury and inhibit disease progression in patients with stable coronary heart disease and evidence of high-risk coronary plaque defined by 18F-fluoride uptake on positron emission tomography.

1.3 RATIONALE FOR STUDY

The rationale for this study is based on two main observations relevant to the pathogenesis of coronary artery disease.

1. The majority of episodes of plaque rupture are subclinical because thrombus formation is non-occlusive and microembolism causes covert myocardial micro-injury that is insufficient to cause overt symptoms.
2. Cycles of rupture and non-occlusive thrombus formation lead to plaque expansion and coronary artery disease progression.

These two features can now be tracked using a high-sensitivity cardiac troponin I assay and computer tomography coronary angiography respectively.

Given this central role of thrombosis in atherogenesis, anti-thrombotic interventions have major potential to impact on the consequences and progression of atherosclerotic disease [Williams *et al*, 1997; Rioufol *et al*, 2004; Kwon *et al*, 2005]. With the advent of more potent platelet inhibition with ticagrelor, there is now the opportunity to assess whether dual anti-platelet therapy can improve markers of myocardial injury and disease progression.

To enhance the opportunity to detect such effects, we propose a stratified medicine approach where we will specifically select patients who have evidence of high-risk or subclinical ruptured coronary artery plaque identified by coronary 18F-fluoride uptake. We will then compare outcomes between those with and those without uptake, anticipating that only patients with high-risk plaque will demonstrate evidence of reduced injury and disease progression.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine whether ticagrelor will reduce plasma high-sensitivity troponin concentrations compared with placebo in patients with stable coronary heart disease and high-risk coronary atheroma.

2.1.2 Secondary Objectives

a) To assess whether ticagrelor will reduce plasma high-sensitivity troponin concentrations in patients without increased coronary 18F-fluoride uptake.

b) To assess whether ticagrelor will reduce plasma high-sensitivity troponin concentrations over a 1-year time frame.

c) To assess whether ticagrelor will reduce coronary plaque volume or calcium score at the site of 18F-fluoride uptake.

d) To confirm the reproducibility of 18F-fluoride PET positivity

e) To assess the natural history of 18F-fluoride PET positive coronary plaque

2.1.3 Safety Objective

To determine whether the addition of ticagrelor to standard optimal medical therapy is safe and well tolerated in patients with stable coronary heart disease on optimal medical therapy. All bleeding events will be categorised according to the previous PLATO criteria [Wallentin *et al*, 2009] and recorded on the CRF.

2.1.4 Exploratory Objectives

The study design will also allow us to establish the effect of ticagrelor on disease progression. Using the baseline and repeat computed tomography coronary angiograms, we will be able to investigate changes in plaque burden, calcium score and lesion severity alongside the end points described above. This will be assessed throughout the coronary circulation as well as specifically at the site of 18F-fluoride uptake. As a measurement of treatment compliance and efficacy, we will also assess platelet-monocyte aggregates before and after *in vitro* stimulation with 20 μm adenosine diphosphate [Frelinger *et al*, 2011].

We will also record details of cardiovascular events occurring during the period of the study to allow an exploration of the association between 18F uptake, treatment allocation and clinical events.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Plasma high sensitivity cardiac troponin I (hsTnI) concentration at 30 days in patients with coronary 18F-fluoride uptake.

2.2.2 Secondary Endpoints

a) Plasma hsTnI concentrations at 30 days in patients without coronary 18F-fluoride uptake.

b) High sensitivity cardiac troponin I (hsTnI) concentration at 30 days in total study population.

c) Plasma hsTnI concentrations over 1 year

d) Calcium score at 1 year

e) Plaque volume at 1 year

f) Reproducibility of 18F-fluoride uptake detected on PET imaging at 1 week

g) Natural history of 18F-fluoride uptake over 1 year

3 STUDY DESIGN

3.1 RATIONALE FOR STUDY DESIGN, DOSES AND CONTROL GROUPS

The study will be a randomised double blind placebo-controlled trial to ensure a rigorous study design and the avoidance of systematic biases of outcome measures. All recruited patients will undergo computed tomography coronary angiography and 18F-fluoride positron emission tomography (PET) scanning at baseline. Patients will then be randomized to ticagrelor 90 mg or matched placebo twice daily [Wallentin *et al*, 2009]. The dose has been selected on the basis of the PLATO trial [Wallentin *et al*, 2009]. The control groups will be two-fold. First there will be the active and inactive comparators of ticagrelor and placebo. Second we will examine for the presence and magnitude of an effect in the groups of patients with or without coronary 18F-fluoride uptake.

The primary outcome will be the comparison between ticagrelor and matched placebo on the change in plasma troponin concentration from baseline to one month in patients with coronary 18F-fluoride uptake. Secondary analyses will undertake the same assessment in patients without coronary 18F-fluoride uptake to determine whether this is particular to patients with high-risk coronary plaque or is seen in all patients with multivessel coronary artery disease.

Further longitudinal comparisons of these groups will determine whether the dominant effect on plasma troponin concentrations is seen only in the early phase or whether potential benefits are seen throughout the study period. Finally, we will assess whether in comparison to placebo, ticagrelor will inhibit progression of coronary atheroma (calcium score and plaque volume) at the site of high-risk coronary plaque.

An additional exploratory component to the study will be to assess the reproducibility and natural history of 18F-fluoride uptake within coronary plaques. This will be investigated with repeat PET scanning within a subgroup of the total population.

4 STUDY POPULATION

4.1 Number Of Participants

We will recruit 220 patients with stable coronary heart disease from the Edinburgh Heart Centre.

4.2 Inclusion Criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Patients aged ≥40 years with angiographically proven multivessel coronary artery disease defined as at least two major epicardial vessels with any combination of either (a) >50% luminal stenosis, or (b) previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery).
2. Provision of informed consent prior to any study specific procedures
3. Receiving aspirin

4.3 Exclusion Criteria

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

1. An acute coronary syndrome within the last 12 months
2. An indication for dual anti-platelet therapy, such as drug eluting stent
3. Receiving thienopyridine therapy such as clopidogrel or prasugrel
4. Percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3 months
5. Inability or unwilling to give informed consent
6. Women who are pregnant, breastfeeding or of child-bearing potential (women who have experienced menarche, are pre-menopausal and have not been sterilised) will not be enrolled into the trial
7. Known hypersensitivity to ticagrelor or one of its excipients
8. Active pathological bleeding or bleeding diathesis
9. Significant thrombocytopenia: platelets <100 x 10^9 /L
10. History of intracranial haemorrhage
11. Moderate to severe liver impairment (Child's Grade B or C)
12. Maintenance therapy with strong CYP3A4 inhibitors, such as ketoconazole, nefazodone, ritonavir, indinavir, atazanavir, or clarithromycin
13. Major intercurrent illness or life expectancy <1 year
14. Renal dysfunction (eGFR ≤30 mL/min/1.73 m^2)
15. Contraindication to iodinated contrast agents
16. Planned coronary revascularization or major non-cardiac surgery in the next 12 months
17. Maintenance therapy with simvastatin or lovastatin at doses greater than 40mg daily
18. Receiving oral anticoagulants including warfarin, rivaroxaban, dabigatran or apixaban.

4.4 Co-Enrolment

Co-enrolment with another clinical trial of an investigational medical product or of a trial involving the use of an additional anticoagulant (e.g. warfarin, dabigatran, rivaroxaban or

apixaban) or antiplatelet (e.g. clopidogrel, prasugrel) will not be allowed with this study. A minimum of 4 months must elapse between studies of this nature prior to patient being eligible.

Co-enrolment involving trials not excluded above will be allowed provided this is not expected to place undue burden upon participants and their families. Consideration will also be given to the total exposure to ionising radiation should additional studies require further exposure.

Co-enrolment with another CTIMP will require written agreement between the Chief Investigator and Trial Steering Committees of the respective trials as well as the trials Sponsors and will be performed in accordance with the ACCORD guidelines for co-enrolment (GL001).

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients will be identified by their usual care team from outpatient clinics and existing clinical databases (the Tomcat and TrakCare databases). They will initially be approached (either verbally or in writing) for study recruitment by their usual care team who are based at the Edinburgh Heart Centre. Patients will be provided with a Patient Information Sheet and given an opportunity to ask questions about participation in the trial.

5.2 CONSENTING PARTICIPANTS

After 2 days, patients willing to participate in the trial will be asked to attend a consent and screening visit at the Clinical Research Facility, Edinburgh. Written informed consent will be obtained by a suitably qualified member of the research team before any study related procedures are performed. Patients will be advised to inform their physicians and dentists that they are enrolled on the study before any surgery is scheduled and before any new medicinal product is taken.

5.3 SCREENING FOR ELIGIBILITY

Screening of clinical records for eligibility will be performed after written consent is obtained. If eligibility cannot be confirmed based on pre-existing clinical investigations (i.e. standard clinical biochemical and haematological variables have not been assessed within the past 6 months) then blood tests will be obtained to assess these variables. Once a patient has agreed to participate and is deemed eligible they will be invited to attend the baseline visit.

Baseline assessments will include clinical history and examination, review of patient records to confirm study eligibility and record clinical profile, standard clinical biochemical and haematological variables, plasma high sensitivity cardiac troponin I measurement, 12-lead electrocardiogram, 18F-fluoride positron emission tomography, computed tomography coronary calcium score and angiography, and storage of plasma, serum and DNA for future analysis.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible and non-recruited patients will receive standard medical care. An anonymised log will be kept of patients who were screened for the study and subsequently found to be ineligible or not recruited.

5.5 PROCEDURES FOR HANDLING SUBJECTS INCORRECTLY ENROLLED, RANDOMISED OR INITIATED ON INVESTIGATIONAL MEDICINAL PRODUCT

Patients incorrectly randomized to the wrong treatment group will be maintained on allocated therapy unless blinding has been compromised. Given that this is a mechanistic study and not a clinical endpoint trial, they will be assigned to the treatment they actually received as part of

the statistical analysis. Records will be kept of the treatment they were originally assigned to, and the treatment they received.

After the first 30 and 90 patients have been randomized into the trial, ECTU will check to ensure that minimization has achieved matching of the two treatment groups.

5.6 RANDOMISATION

5.6.1 Randomisation Procedures

Eligible patients will be randomized using a web-based randomization service to ensure allocation concealment. Given the modest sample size, we will minimise treatment allocation according to age, sex, baseline plasma troponin concentration and the presence of coronary 18F-fluoride uptake.

5.6.2 Treatment Allocation

The placebo and active medication will be presented in numbered packages in collaboration with the Investigational Supplies Group (University of Edinburgh).

5.6.3 Methods to Ensure Blinding

The inactive placebo comparator will be presented and packaged in a form that will be indistinguishable from the active medication, ticagrelor. Therefore the treating clinical staff and patient will be blind to the allocated treatment. An indication of treatment allocation will potentially be apparent with platelet-monocyte aggregate testing. This will be undertaken by a dedicated technician distinct from the clinical investigational team. Samples will be presented to the technician using anonymised sample codes. Results will be stored in the database but not released to the study investigators until the end of the trial.

5.6.4 Emergency Unblinding Procedures

Web-based computer randomisation software will generate a randomisation list based on the values used for minimisation. This list will then be provided to the Investigational Supplies Group (ISG) for drug labelling purposes. The randomisation software will also contain unblinding codes which can only be accessed using a username and password. A username and password will only be provided to the Sponsor and Pharmacy department and can be used if emergency unblinding is required. Requests for unblinding will either go through the Chief or Principal Investigator and unblinding will be performed as required by the duty Pharmacist.

5.6.5 Discontinuation of Investigational Medicinal Product

The investigational product will be discontinued under the following circumstances:

1. At the request of the patient or if the patient withdraws from the study.
2. By the investigator or the responsible clinician if this was felt to be in the best interests of the patient.
3. On completion of the study.

Brief interruptions of therapy will be permitted (<14 days) where there is a clinical need, such as unavoidable surgical intervention. In such circumstances, the IMP will be withdrawn 5 days prior to surgery and recommenced as appropriate by the clinical team.

5.6.6 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form. The patient will have the option of withdrawal from (i) the repeat PET and CT sub-study only (ii) study medication with continued study procedures and

collection of clinical and safety data (iii) all aspects of the trial but continued use of data collected up to that point, (iv) all aspects of the trial with removal of all previously collected data.

Randomised patients who wish to be withdrawn from the study before they have provided a blood sample for the assessment of plasma troponin concentration at one month of the trial, will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the database.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor (AZD6410)	90 mg tablet	Astrazeneca

6.1.1 Study Drug Identification

Ticagrelor is presented as a round biconvex film-coated yellow tablet marked with Œ90¹ above Œ T¹ on one side.

6.1.2 Study Drug Manufacturer

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje

SWEDEN

6.1.3 Marketing Authorisation Holder

AstraZeneca AB
S-151 85
Södertälje
Sweden

MA number EU/1/10/655/001-006

6.1.4 Labelling and Packaging

Astra Zeneca will supply study medication and placebo in prefilled HDPE bottles with Child resistant caps. The HDPE bottles will be clearly labelled for the purpose of this trial including the study title, trial subject number and study contact by the Investigational Supplies Group, Edinburgh (ISG).

A Qualified Person from ISG will then release the study drug to the Pharmacy Department at the Royal Infirmary of Edinburgh.

6.1.5 Storage

All study medication will be kept in a secure place under appropriate storage conditions in the Pharmacy Department at the Royal Infirmary of Edinburgh.

6.2 PLACEBO

Astra Zeneca will supply a matched placebo in prefilled HDPE bottles with Child resistant caps. The placebo will then be labelled by ISG and released to the Pharmacy Department at the Royal Infirmary of Edinburgh.

6.3 DOSING REGIME

One tablet twice daily for 12 months.

6.4 DOSE CHANGES

No alteration in the planned dosing regime will be allowed.

6.5 PARTICIPANT COMPLIANCE AND ACCOUNTABILITY

Members of the research team will assess treatment compliance at attendance of each of the study visits by interview and pill count. Non-compliance with the dosing regime will only be considered a protocol deviation if the participant takes less than 90% of the planned dose. Any unused study medication will be returned to the Pharmacy Department at the Royal Infirmary for destruction.

6.6 OVERDOSE

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses.

In the event of overdose, we will observe for these potential adverse reactions and consider ECG monitoring. There is currently no known antidote to reverse the effects of ticagrelor and it is not expected to be dialysable. Treatment of overdose will follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures will be taken.

If an overdose occurs in the course of the study, the investigators or other site personnel will inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

18F-Sodium Fluoride (18F-NaF)

At the time of positron emission tomography and computed tomography coronary angiography, patients may receive oral and/or intravenous beta-blockade, such as metoprolol 5-100 mg, to slow the heart rate to below 65 beats per minute to maximise image quality and reduce radiation exposure. Glyceryl trintrate spray or tablet will be administered sublingually (200-400 µg) to induce coronary vasodilatation to enhance image quality of the coronary angiogram.

6.7.2 Permitted Medications

All patients will be maintained on aspirin 75 mg once daily and maximally tolerated dose of statin. Patients will be encouraged to be maintained on maximally tolerated doses of angiotensin-converting enzyme inhibition and beta-blocker therapy as clinically indicated and

in accordance with local guidelines. Following completion of the study, the trial medications will be discontinued.

6.7.3 Prohibited Medications

- Strong CYP3A4 inhibitors, such as ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir.Thienopyridines such as prasugrel, clopidogrel and ticlopidine
- Coumarin anticoagulants such as warfarin
- Direct thrombin inhibitors such as dabigatran
- Factor Xa inhibitors such as rivaroxaban and apixaban
- Ergot alkaloids
- Cisapride
- Simvastatin or lovastatin when taken at doses >40 mg daily

7 STUDY ASSESSMENTS

Trial participants will undergo 8 study visits: screening visit, baseline, randomisation and after 1, 3, 6, 9 and 12 months.

7.1 SAFETY ASSESSMENTS

The study does not have any pre-specified safety outcome measures. However, all bleeding events will be categorized according to the previous PLATO criteria [Wallentin *et al*, 2009]. These will be reported through adverse event reporting mechanisms (see Section 10).

7.2 STUDY ASSESSMENTS

This is a prospective single-centre randomized double blind matched placebo controlled trial of ticagrelor 90 mg twice daily in patients with stable coronary artery disease for 1 year. Subjects will attend for clinical assessments at 30 days, 3, 6, 9 and 12 months with a final computed tomography coronary angiogram at the end of the study. The randomisation visit must be conducted within 25 days of the baseline visit.

	Screening -183 days	Baseline (-15 days ±10 days)	Randomisation (Day 0)	30 days (±5 days)	3 months (±14 days)	6 months (± 14 days)	9 months (± 14 days)	1 year (± 14 days*)
Eligibility Criteria and PIS	X							
Continuing eligibility confirmed			X	X	X	X	X	
Consent	X							
Concomitant medications		X		X	X	X	X	X
Clinical History		X		X	X	X	X	X
Physical Examination		X						
Clinical Biochemistry and haematology	X (if not checked in past 6 months)	X					X	
Blood sampling for hsTnI		X		X	X	X	X	X
Blood sampling for PMA		X		X				
12-lead ECG		X		X	X	X	X	X
AE/SAE Reporting		X		X	X	X	X	X
Treatment allocation/Medication dispensed			X		X	X	X	
Compliance check				X	X	X	X	X
18F-Fluoride PET		X	X		X	X		X
			Additional 18F-Fluoride PET scans will be performed in a subgroup only					
CT attenuation correction								
			CT attenuation correction is required prior to each PET scan for the subgroups who undergo this					
CT Calcium Score		X						X
CT Coronary Angiogram		X	Repeat CTCA scans will be performed at the time of each PET scan for those who are in the reproducibility and natural history sub-studies					X*

* Where it is not possible for the CT scan at the 1 year visit to be performed at the same time as the other 1 year study assessments participants may be asked to attend an additional visit during which the CT scan will be performed. In this situation the remainder of the study assessments will be performed within the planned visit window (± 14 days) and the CT scan will be arranged for the earliest practicable opportunity.

7.2.1 Baseline Assessments

Baseline assessments will include clinical history and examination, review of patient records to confirm study eligibility and record clinical profile, standard clinical biochemical and haematological variables, plasma high sensitivity cardiac troponin I measurement, platelet-monocyte aggregates, 12-lead electrocardiogram, 18F-fluoride positron emission tomography,

computed tomography coronary calcium score and angiography, and storage of plasma, serum and DNA for future analysis.

7.2.2 Follow Up Assessments

At 1, 3, 6, 9 and 12 months, participants will undergo repeat clinical assessment, blood sampling, and 12-lead electrocardiogram. Compliance will be recorded by patient history and tablet count by a delegated member of the research team. At the final study visit (12 months), subjects will also undergo a repeat computed tomography coronary calcium score and angiography.

Where it is not possible for the CT scan at the 12 month visit to be performed at the same time as the other 12 month study assessments participants may be asked to attend an additional visit during which the CT scan will be performed. In this situation the remainder of the study assessments will be performed within the planned visit window (± 14 days) and the CT scan will be arranged for the earliest practicable opportunity.

7.2.3 High Sensitivity Cardiac Troponin I

Plasma cardiac troponin I concentrations will be measured by the accredited Clinical Biochemistry Department of the Royal Infirmary of Edinburgh using the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL). This is the first commercially available high-sensitivity troponin I assay that has greater precision at very low concentrations compared with the contemporary assay. The limit of detection is 1.2 ng/L and the inter-assay coefficient of variation <10% at 4.7 ng/L. The upper reference limit (99th percentile) based on 4,590 samples from healthy men and women is 34 ng/L for men and 16 ng/L for women.

7.2.4 Positron Emission and Computed Tomography Coronary Angiography

Study scans will be performed in the Clinical Research Imaging Centre.

Patients with a heart rate exceeding 65 beats/min may receive intravenous or oral beta-blockade (e.g. 5 to 100 mg metoprolol) 1 h before computed tomography. All patients will receive sublingual glyceryl trinitrate (200-400 µg) just prior to the computed tomography coronary angiography.

All patients will undergo dual cardiac and respiratory-gated positron emission and computed tomography imaging of the coronary arteries with a hybrid scanner (64-multidetector Biograph mCT, Siemens Medical Systems, Erlangen, Germany). Study subjects will be administered a target dose of 250 MBq 18F-fluoride intravenously and subsequently rested in a quiet environment for 60 min. An attenuation correction computed tomography scan (non-enhanced 120 kV and 50 mA) will then be performed, followed by positron emission tomography imaging of the thorax in list-mode for 30 min.

Computed tomography coronary calcium score and angiography will be undertaken in the same visit as the 18F-floride scan and again at 1 year. With the patient lying still on the scanner after acquisition of the positron emission tomography scan, an electrocardiogram-gated breath-hold computed tomography scan (non-contrast-enhanced, 40 mAs/rotation, 120 kV; CareDose, Siemens Medical Systems) of the coronary arteries will be performed at the following settings: 330 ms rotation time, 100 (body mass index [BMI] <25 kg/m^2) or 120 (body mass index >25 kg/m^2) kV tube voltage, 160-245 mAs tube current, 3·8 mm/rotation table feed, prospective (heart rate regular and <60/min), or retrospective (heart rate >60 /min) electrocardiogram-gated. Depending on the BMI, a bolus of 80-100 mL of contrast (400 mgI/mL; Iomeron, Bracco, Milan, Italy) will be injected intravenously at 5 mL/s, after determining the appropriate trigger delay with a test bolus of 20 mL contrast material.

The positron emission tomography scans will be reconstructed in multiple phases of the cardiac cycle, with the diastolic phase (50-75%) used for analysis. The computed tomography coronary angiography scans will be reconstructed at 0·75 x 0·7 mm and 0·6 x 0·3 mm for retrospective and prospective acquisitions respectively at 60%, 65% and 70% of the cardiac cycle. Additional reconstructions will be undertaken as necessary. Positron emission tomography scans will correct for cardiac motion correction using electrocardiogram-gated images.

18F-F PET Natural History Sub-study

Using the same scan process as outlined above a sub-group of patients will be selected for 1 additional PET scan. In total this will involve 80 patients out of the total cohort. The first 20 participants to be scanned will be to assess the reproducibility of 18F-fluoride uptake and will undergo a second PET scan at the randomisation visit (1 week after the baseline scan). This group will comprise 10 patients from both of the PET positive and PET negative samples. Following this we will investigate the natural history of 18F-fluoride uptake by performing repeat PET scans on 60 patients in total from the initial PET positive sample with 20 patients scanned at the 3 month, 6 month and 12 month follow up visits. No individual patient will undergo more than 2 PET scans during the course of the study. In order to allow accurate co-registration of images, repeat CT coronary angiograms will be performed at the time of the repeat PET scans. The additional PET scan for those in the sub-study will be performed at the 1 week, 3 month, 6 month or 12 month visit but the additional CTCA scan will only be performed at 1 week, 3 month or 6 month visits as the CTCA scan at 12 months will be performed on all participants irrespective of whether they are taking part in the sub-study

7.2.5 Platelet-Monocyte Aggregates

The effect of ticagrelor on platelet activation will be assessed before and after *in vitro* stimulation with 20μm adenosine diphosphate to assess inhibition of the $P2Y_{12}$ receptor [Harding *et al*, 2007; Burdess *et al*, 2010; Frehling *et al* 2011]. This will be performed at the baseline visit (before study medication ingestion) and at the 30 day visit [Gurbel et al 2009; Frehling et al 2011]. Platelet-monocyte aggregate measurements will be performed by a trained technician independent to the study team to ensure blinding of treatment allocation is not compromised.

Blood will be anticoagulated with D-phenylalanyl-L-prolyl-L-arginine chloromethylketone (PPACK; Cambridge Biosciences, UK). Five minutes after sample collection, samples will be stained with the following conjugated monoclonal antibodies: APC-conjugated CD14 (Becton-Dickinson, UK);, PE-conjugated CD62P (Becton-Dickinson, UK); PE-Cy7-conjugated CD11b(Becton-Dickinson, UK); FITC-conjugated CD42a(Becton-Dickinson, UK); and appropriate control samples prepared. Once stained, samples will be incubated for 20 min at room temperature and fixed with FACS-Lyse (PMA analysis) or paraformaldehyde (platelet analysis). Samples will be analyzed using a FACScalibur flow cytometer (Becton-Dickinson, UK). Platelet–monocyte aggregates will be defined as monocytes staining positive for CD42a, as described previously [Harding *et al*, 2007]. Analysis will be performed using FlowJo (Treestar, USA).

7.2.6 Biological Samples

Blood samples will be collected and tested at baseline, 30 days and 3, 6, 9 and 12 months. At baseline, blood samples will be taken for routine clinical biochemistry and haematology (including full blood count, urea, creatinine and electrolytes, liver function tests, total cholesterol and glucose).

Approximately 20 mL of blood will be obtained on each visit except that an additional 20 mL will be taken at baseline for the clinical biochemistry and haematology assessments. Blood will also be stored for DNA extraction for subsequent analysis as appropriate.

Blood samples will be processed and stored in the Clinical Research Facility. Blood sample will be processed (plasma and serum) and stored at -80°C for later analysis of potential extracellular matrix and inflammatory biomarkers. Blood will also undergo DNA extraction and flow cytometric assessment for platelet monocyte aggregates [Burdess *et al*, 2010].

All samples will be stored in locked secure freezers and in compliance with the sponsor's tissue governance policies.

All samples will be retained unless consent is withdrawn by the participant who specifically requests that their samples are destroyed.

8 DATA COLLECTION

All trial data will be recorded onto written case record forms (CRF) by a member of the research team and then entered into electronic CRFs designed and developed by the Edinburgh Clinical Trials Unit.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Patients with increased 18F-fluoride activity had plasma high-sensitivity troponin concentrations that were more than double those of patients without increased 18F-fluoride uptake (7.89±9.34 versus 3.10±1.89 ng/L; P=0·047) in our recent trail [Joshi et al, 2013]. Based upon the assumption that ticagrelor will reduce plasma high sensitivity troponin concentrations by one half (i.e from 7.89 to 3.95 ng/L, with standard deviations of 9.34 and 1.89 respectively), we will require 48 patients per treatment arm at 80% power and two-sided P<0.05. Allowance for missing data brings this to 55 per group. Following review of the first 170 PET scans within the DIAMOND study, the proportion of patients who demonstrate coronary tracer uptake is 60%. Consequently we will need 183 patients with follow-up data available for the primary endpoint. In order to allow for participant withdrawal prior to the 30-day visit we will recruit a total of 220 patients.

The Edinburgh Heart Centre performs more than 5,000 diagnostic angiograms and 2,500 angioplasty procedures per year. This should allow an adequate pool of potentially suitable patients with angiographically proven stable coronary artery disease from which to recruit.

9.2 PROPOSED ANALYSES

9.2.1 Description of Analysis Sets

The primary analysis will be to determine whether ticagrelor will reduce plasma high-sensitivity troponin concentrations compared with placebo in patients with stable coronary heart disease and increased coronary 18F-fluoride uptake. For this primary analysis, we will exclude any patient who does not have a blood sample for estimation of the one-month plasma troponin concentration or whose compliance is deemed inadequate (as estimated from pill counts). The required level of medication compliance will be described in the statistical analysis plan.

9.2.2 Methods of Statistical Analysis

For the primary analysis, the change in plasma high-sensitivity troponin concentration from baseline to 30 days will be compared between the two treatment groups (ticagrelor and placebo) using linear regression, adjusting for the minimisation variables, in patients with coronary 18F-fluoride uptake. Prior to analysis, tests for normality will be undertaken and, where data are skewed, logarithmic transformation will be considered prior to analysis. Effect sizes and 95% confidence intervals will be calculated. Similar analyses will be performed for the assessment of troponin at 30 days in patients without coronary 18F-fluoride uptake, and in the study population as a whole; for troponin at 1 year; and for calcium score and plaque volume at 1 year at the site of baseline coronary 18F-fluoride uptake.

Statistical analysis will be performed using SAS. A two-sided P<0·05 will be taken as statistically significant. A full statistical analysis plan will be documented prior to data base lock. This will be overseen by the trial statistician in the Edinburgh Clinical Trials Unit.

10 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. After initially recording an AE, the Investigator should follow each AE until resolution of the event or until no longer medically indicated.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

10.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until the last study visit.

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) will be unblinded.

The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the Summary of Product Characteristics.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC/IB.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC/IB.

Unexpected: the AR is not consistent with the toxicity in the SmPC/IB.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

10.7 ASTRA ZENECA REPORTING REQUIREMENTS

All SAEs will be reported to AstraZeneca within 7 days, whether or not considered causally related to the investigational product.

The report will indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

A cover page/the SAE report will detail the following:

- Investigator Sponsored Study (ISS)
- The Investigator IND number assigned by the FDA
- The Investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

The SAE report will be sent [with the accompanying cover page] by fax to AstraZeneca's designated fax line: 01582 838 010 or by email to: CRGSAERportingGlobalStudies@astrazeneca.com

10.8 FOLLOW UP PROCEDURES

After recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

After initially recording an AE, the Investigator should follow each AE until resolution of the event or until no longer medically indicated.

11 PREGNANCY

Woman of child-bearing potential will not be enrolled into the trial (woman who have experienced menarche, are pre-menopausal, have not been sterilised or who are currently pregnant).

Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and partners of male participants will be followed up until following the outcome of the pregnancy.

All outcomes of pregnancy will be reported to AstraZeneca.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh) and a coordinating Clinical Research Facility nurse.

The Principal Investigator will oversee the study and will be accountable to the Chief Investigator. The Principal Investigator will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The review of SAEs will be added to the TSC agenda to ensure that appropriate action is taken if any safety issues arise.

12.3 DATA MONITORING COMMITTEE

In the PLATelet inhibition and patient Outcomes (PLATO) trial of 18,624 patients presenting with an acute coronary syndrome, ticagrelor was superior to clopidogrel for the prevention of cardiovascular events and death [Wallentin *et al*, 2009]. There were modest increases in the risks of bleeding and low rates of other side effects, such as dyspnoea. It is extremely unlikely that we will observe any substantial increased risk in our trial population given the small sample size of 250 patients and the very similar disease population in the PLATO trial that had a 100-fold larger trial population size. For this reason, an independent Data Monitoring Committee (DMC) will not be convened for this study and all study adverse events will be reported to the sponsors and AstraZeneca and will be discussed by the TSC.

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

12.6 BENEFIT/RISK BALANCE

12.6.1 Benefits

Patients may benefit from the treatment intervention. The benefits of ticagrelor in addition to standard medical therapy may include a reduction in the consequences and progression of coronary artery disease. In the PLATO trial [Wallentin *et al*, 2009], there appeared to be an ongoing and continuous improvement in outcomes beyond three months of an acute coronary syndrome. Ticagrelor may therefore have important ongoing secondary preventative benefits even in patients with apparently stable coronary artery disease. This is the rationale for the ongoing trial of the prevention of cardiovascular events in patients with prior myocardial infarction using ticagrelor compared with placebo on a background of aspirin: the PEGASUS trial (NCT01225562).

Patients may also benefit from additional procedures and investigations that they will undergo as part of the study. This will include closer medical supervision and non-invasive imaging investigations that may identify important incidental findings.

12.6.2 Risks

The risks of ticagrelor principally relate to bleeding, transient bradyarrhythmias and dyspnoea. As with most anti-thrombotic treatments, there is a risk of excess bleeding. The incidence of excess major bleeding was modest and we will ensure robust exclusion criteria to prevent inclusion of patients at risk of bleeding. Bradyarrhythmias have been described but are generally transient and do not require intervention. We will record 12-lead electrocardiograms at subject visits and question patients regarding symptoms of dizziness and syncope. For

dyspnea, there is a 14% rate of breathlessness associated with ticagrelor in the PLATO trial [Wallentin *et al*, 2009]. However, again this is usually mild and self-limiting, and discontinuation of study medication was necessary in only 1% of patients.

There are some potential hazards of the non-invasive investigations that we will perform as part of the trial. The main issues relate to exposure to ionising radiation and contrast agent administration. We have a well-developed protocol for cardiac positron emission and computed tomography imaging that minimizes radiation exposure and has clear procedures for managing adverse contrast reactions. We anticipate that the total research protocol dose (TPRD) radiation exposure will be 30 mSv. The TRPD includes radiation exposure from both the PET and CT scans combined. The estimated associated risk of developing fatal cancer is proportional to dose. Using a risk of 5% per Sv [ARSAC Notes] in a healthy population in this age group the estimated associated risk of developing fatal cancer as a result of this exposure is in the region 1 in 650. This risk can be classified as moderate. It is likely that in a population of any patients in the age group 40-50 years the cancer risk is approximately 5% per Sv (and correspondingly less than 5% per Sv as age increases above 50 years). For comparison the average annual background radiation dose arising from natural sources of ionising radiation in the environment in the UK is 2.2 mSv. The TRPD of 30 mSv incurred in this study is approximately 13-14 times annual background radiation from natural sources. An objective of this study is to assess reproducibility of NaF PET/CT. A subgroup of 80 subjects will receive a second PET/CT and additional CT coronary angiogram. This increases the TRPD to 46 mSv in those subjects that have their repeat scan at the randomisation visit, 3 months or 6 months and to 38mSv in those that undergo their repeat scan at 12 months. The associated risk of developing cancer as a result of this exposure is in the region of 1 in 450. This risk can be classified as moderate. A TRPD of 46 mSv is approximately 21 times annual background radiation from natural sources in the UK. All subjects will have two CT coronary angiograms and those in the sub-studies returning at the randomisation visit, 3 months or 6 months will have 3 CT coronary angiograms. We note that in occasional individual cases the effective dose from CT coronary angiography may increase to approximately 20 mSv, if the subject's heart rate cannot be kept sufficiently low, requiring an alternative retrospective gating technique to be used. This will add approximately 12 mSv to the total research protocol dose for all subjects having CTCA.

This can be compared with other commonly used cardiovascular imaging techniques, such as nucleotide myocardial perfusion imaging (15-20 mSv) and diagnostic coronary angiography (7 mSv) [Einstein *et al*, 2007]. The risks of exposure to the contrast medium include allergic reactions and impairment of kidney function. Amongst patients with moderate-to-severe chronic kidney disease, there is a 2-4% risk of kidney impairment after computed tomography angiography [Barrett *et al*, 2006]. The risk of contrast exposure in this study will be minimised by exclusion of high-risk patients who have significant kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2).

12.7 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principle Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);

- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of a urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

14.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.5 END OF STUDY

It is anticipated that the study will last 3 years: two years for recruitment and one year of follow-up. The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

The study medication will not be continued at the trial conclusion as it is not currently licensed for use in stable coronary artery disease. Patients will remain eligible to use ticagrelor for any approved indication however (i.e. for 12 months following an acute coronary syndrome).

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating

in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 PEER REVIEW

The study protocol and outcomes data have been reviewed by AstraZeneca who have agreed to help support the conduct and part funding of this clinical trial. There is additional peer review from the Trial Steering Committee and the Edinburgh Clinical Trials Unit statistician as well as the Medical Research Council.

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FIGURE 1 Focal 18f-Fluoride Uptake in Patients with Myocardial Infarction and Stable Angina

Patient with acute ST-segment elevation myocardial infarction with (A) proximal occlusion (red arrow) of the left anterior descending artery on invasive coronary angiography and (B) intense focal 18F-fluoride uptake (yellow-red) at the site of the culprit plaque (red arrow) on the combined positron emission and computed tomogram.

Patient with anterior non-ST-segment elevation myocardial infarction with (C) culprit (red arrow; left anterior descending artery) and bystander non-culprit (white arrow; circumflex artery) lesions on invasive coronary angiography that were both stented during the index admission. Only the culprit lesion had increased 18F-fluoride uptake on combined positron emission and computed tomography (D) following percutaneous coronary intervention.

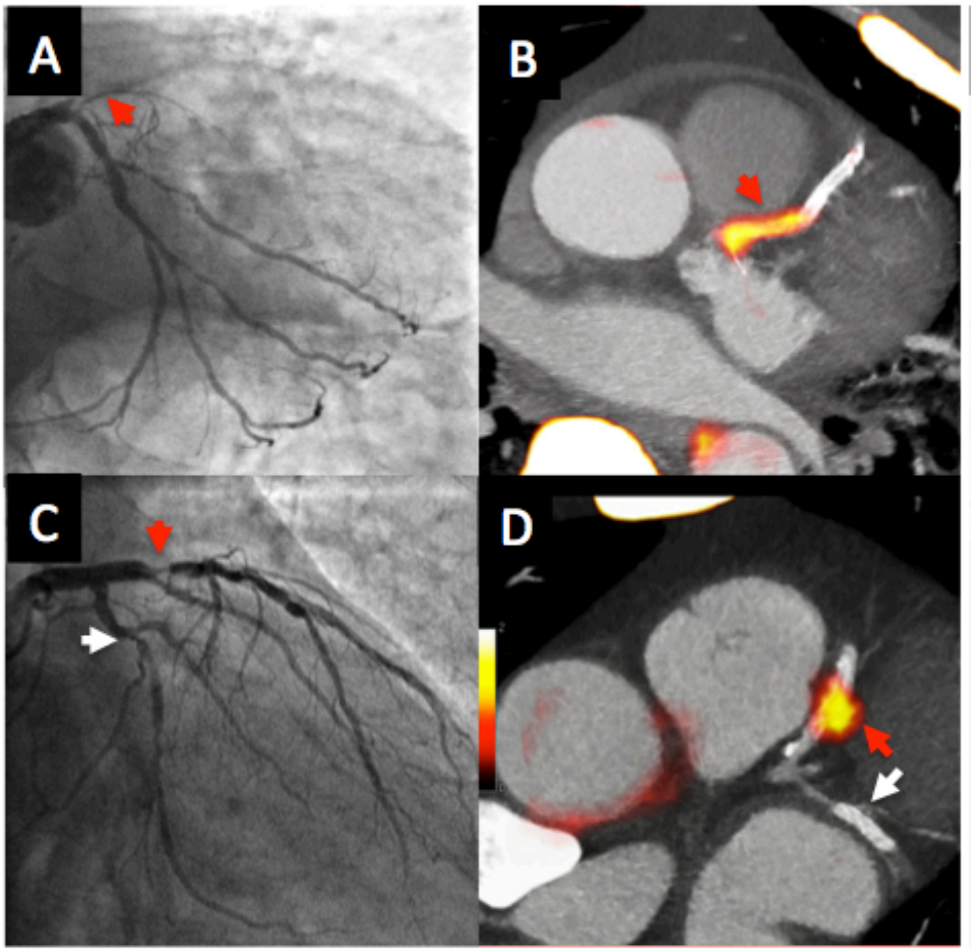


FIGURE 2: Patients with Stable Angina and 18F-Fluoride Uptake

Representative examples for 18F-fluoride uptake in patients with stable angina. Panels A-D, computed tomography coronary angiograms; panels E-H, 18F-fluoride positron emission tomograms; and panels I-L, fused positron emission tomograms and computed tomography coronary angiograms.

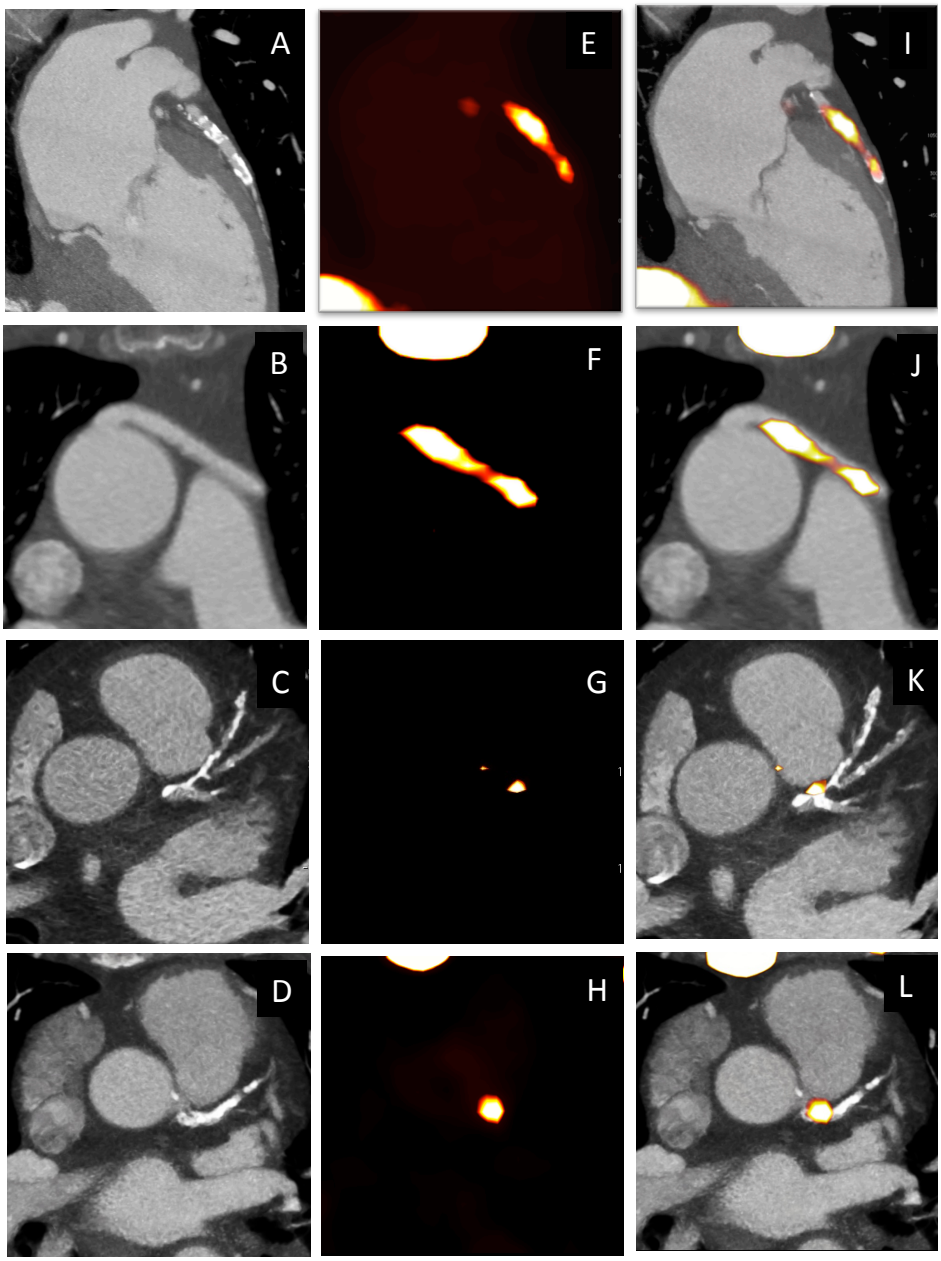
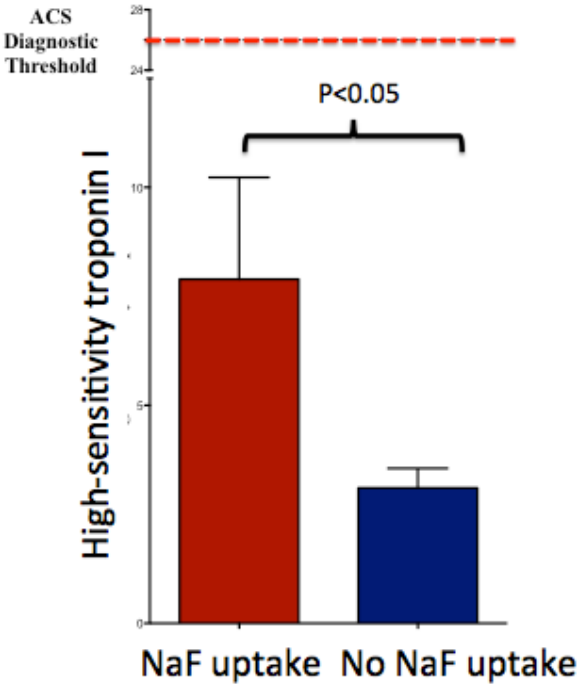


FIGURE 3: High-Sensitivity Troponin I Levels in Patients With Stable Angina Who Have and Do Not Have Increased Coronary 18F-Fluoride Uptake



APPENDIX 1: Trial Investigators

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