Comparative Efficacy of Ticagrelor Versus Aspirin on Blood Viscosity in Peripheral Artery Disease Patients with Type 2 Diabetes

PI: Dr. Robert S. Rosenson
NCT02325466
Document Date: January 19, 2018

Drug Substance	Ticagrelor / BRILINTA / AZD6140
Study Number	ISSBRIL0174
Version Number	~~3~~4
Date	~~22~~19-~~May~~Jan-~~2015~~2018

Comparative Efficacy of Ticagrelor Versus Aspirin on Blood Viscosity in Peripheral Artery Disease Patients with Type 2 Diabetes

Sponsor: Robert S. Rosenson, MD

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

None.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ABI	Ankle brachial index
ASA	Acetylsalicylic acid; Aspirin
ANOVA	Analysis of Variance
BID	Twice a day
CVD	Cardiovascular disease
cP	Centipoise
DM	Diabetes mellitus
mg	Milligrams
MI	Myocardial infarction
OD	Oral dose
PAD	Peripheral artery disease
s^{-1}	Inverse seconds; shear rate
WBV	Whole blood viscosity

1. INTRODUCTION

1.1 Background

Ticagrelor is a cyclopentyltriazolopyrimidine that has been shown to reduce significantly the rate of cardiovascular disease (CVD) events and death compared with clopidogrel in 18,624 patients having prior acute coronary syndrome [1]. The adenosine diphosphate receptor P2Y12 antagonist, clopidogrel 75 mg was more effective than aspirin 325 mg in reducing CVD events or death in a clinical trial of 19,185 patients with atherosclerosis, presenting with symptomatic peripheral artery disease (PAD), recent ischemic stroke or myocardial infarction (MI) [2]. In a pre-specified analysis of risk by the type of vascular events at entry, there was no reduction in MI, stroke or cardiovascular death rates in patients who entered the trial with an ischemic stroke or MI while there was a relative risk reduction of 23.8% (p=0.0028) in the group entering the trial with symptomatic PAD. The disproportionate event reduction in patients with PAD patients suggests that mechanisms other than atherosclerosis or thrombosis may contribute to CVD event reduction in these patients. Of the possible mechanisms, blood rheology is an important factor that influences macrovascular and microvascular flow in lower extremity arteries, and predicts CVD events in PAD patients.

1.2 Research hypothesis

Both aspirin-ticagrelor and ticagrelor monotherapy will be superior to aspirin monotherapy in the reduction of whole blood viscosity at the end of each 4 week treatment period.

1.3 Rationale for conducting this study

A previous study comparing 120 patients having intermittent claudication with normal age-matched controls found blood viscosity was significantly higher among claudicants ($p<0.001$) with the greatest difference in blood viscosity observed at lowest shears [3]. At high shear rates, patients with blood viscosity above 4.5 cP had mean claudication distance of 126 meters compared to 289 meters for patients with high-shear viscosity below that threshold. This report suggested the use of the term rheological claudication to describe approximately 25% of moderate to severe claudicants with hyperviscosity of blood having significantly worse prognoses.

In a random sample of 1,581 men and women 55 to 74 years of age with symptomatic or asymptomatic PAD, whole blood viscosity and fibrinogen were independently associated with peripheral arterial narrowing [4]. Plasma viscosity was also associated with claudication. The risk of claudication for patients in the upper quintile of plasma viscosity was 3.4 times greater than the risk for those in the lowest plasma viscosity quintile. The authors implicated blood rheological factors in the pathogenesis of lower limb ischemia in the general population.

The link between blood viscosity and ischemic heart disease events or strokes was reported in a study of a random population of 1,592 adults followed for a mean of 5 years: After adjustment for age and gender, both blood viscosity and hematocrit-corrected blood viscosity were higher in patients who experienced CVD events (myocardial infarction, angina pectoris, coronary revascularization or stroke) than in those who did not. The difference in blood viscosity between the two groups of patients was significant ($p=0.0003$) [5]. A number of outcome studies have demonstrated the risk of major CVD events increased with blood viscosity [6,7]. Stroke patients and those with stroke risk factors were shown to have chronically elevated blood viscosity relative to healthy controls [8].

A number of observational studies have reported increased blood viscosity in type 2 diabetics compared with nondiabetics. In an early clinical study comparing 16 diabetics with 16 age and gender-matched nondiabetic control subjects, mean blood viscosity at low shear rate was observed to be 26% higher in diabetics ($p<0.001$) [9]. A study of 38 male diabetics with and without retinopathy compared against 38 nondiabetics, matched for age and smoking habit, found low-shear blood viscosity levels were on average 13% higher in diabetics without retinopathy and 30% higher in those with retinopathy relative to control subjects [10]. These differences persisted after adjusting for hematocrit. A separate study of 64 diabetics and 61 matched nondiabetics reported similar results: elevated mean viscosity levels in diabetics compared with control subjects and the highest increases in diabetics with retinopathy or nephropathy [11].

Pharmacological therapies for reducing blood viscosity have been limited to clopidogrel [12], aspirin-dipyridamole [13] and in some studies pentoxifylline [14,15]. A reduction in blood viscosity has not been observed with either cilostazol [15] or ticlopidine [16]. In a double-blind, placebo-controlled study of 30 age and gender-matched patients with subclinical carotid or femoral atherosclerosis, clopidogrel was observed to reduce mean low-shear blood viscosity by 18% from baseline levels 3 weeks after administration ($p<0.01$) [12].

1.4 Benefit/risk and ethical assessment

The cross-over study design exposes each randomized group to each of the three treatments, thus reducing treatment bias. Aspirin monotherapy for treatment of PAD is technically an off-label use, however, it is remains a Class I recommendation by the ACCF/AHA Task Force on Practice Guidelines when given in daily doses of 75 to 325 mg as a safe and effective antiplatelet therapy to reduce risk of CVD events in those with symptomatic lower extremity PAD [17]. Patients should be counseled on the importance of not taking aspirin outside of the study because doses greater than 100 mg/day can reduce the efficacy of ticagrelor [18]. When possible, if ticagrelor treatment results in bleeding, the bleeding should be managed without stopping therapy as increased risk of CVD events can occur. Also, patients with history of hyperuricemia, gouty arthritis, hepatic impairment, and renal impairment should be monitored closely if taking ticagrelor.

2. STUDY OBJECTIVES

2.1 Primary objective

(1) Compare the effect of aspirin-ticagrelor with aspirin in a double blind, randomized, cross-over study design (weeks 1-4, weeks 6-10, and weeks 12-16) on blood viscosity at both low (5 s^{-1}) and high (300 s^{-1}) shear rates at the end of each 4-week treatment period.

(2) Compare the effect of ticagrelor monotherapy with aspirin in a double blind, randomized, cross-over study design (weeks 1-4, weeks 6-10, and weeks 12-16) on blood viscosity at both low (5 s^{-1}) and high (300 s^{-1}) at the end of each 4-week treatment.

2.2 Secondary objectives

(1) Determine whether there are differences in low and high shear rate dependent viscosity with treatment by ticagrelor alone and combination aspirin-ticagrelor.

(2) Investigate the effect of the treatment on peripheral arterial blood flow using pulse volume recordings, ankle brachial index, toe pressures and laser flow Doppler (a new emerging technique capable of measuring the velocity of flow and number of cells in the vessel, providing a normalized measure of microcirculatory flow (velocity of flow x number of cells/backscatter)

.

2.3 Safety objective

This study is not designed to compare safety between treatments.

2.4 Exploratory objectives

Not applicable.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

The proposed, double-blind, placebo-controlled, cross-over design study examines and compares the effects of low-dose aspirin, combination aspirin-ticagrelor, and ticagrelor monotherapy on blood viscosity in type 2 diabetes patients with symptomatic PAD who are 18 years of age or older. Study participants will be randomized into 3 groups, and each group will receive each of 3 treatments in the cross-over study. Subjects will be eligible if they have ankle-brachial index less than or equal to 0.85, or if a patient's blood vessels are calcified, patients will have toe-brachial index less than or equal to 0.6 performed using continuous-wave Doppler. Pulse volume recordings will be simultaneously obtained at the level of the ankle, metatarsal and toe bilaterally (Parks Flolab, Parks Medical Electronics, Aloha, OR) according to standard protocol as well as Laser flow Doppler (Perimed Periflux 5000, Perimed AB, Sweden). Subjects will be excluded for planned revascularization or amputation, as well as for known hypersensitivity or allergic reactions to aspirin, bleeding disorders, history of intracranial hemorrhage, and those considered to be at risk of hemorrhagic events will also be excluded from the study. Aspirin 81 mg has been shown to have no significant effect on blood viscosity in healthy individuals [13], and will be used as background therapy prior to randomization; this treatment will serve as comparison for control.

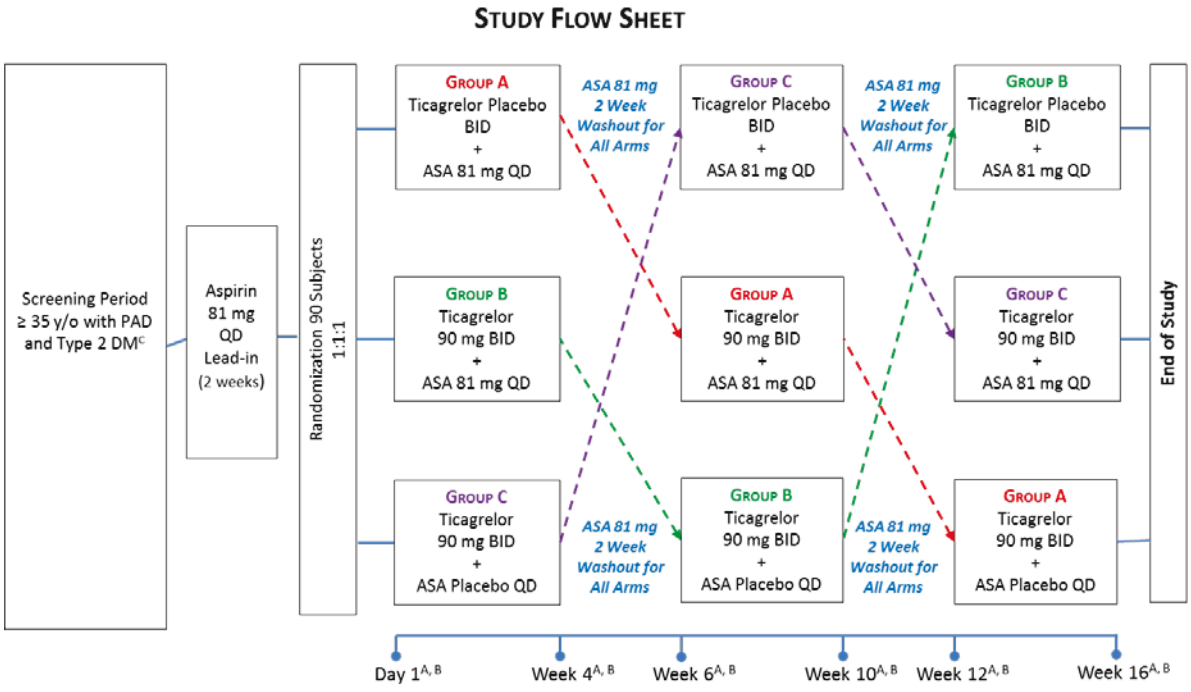
After 2 weeks run-in treatment with aspirin 81 mg daily, patients will be randomized to one of 3 arms (ticagrelor placebo and aspirin 81 mg (Group A), ticagrelor and aspirin 81 mg (Group B), or ticagrelor monotherapy with aspirin placebo (Group C)) and treated for 4 weeks. At this initial visit and every visit thereafter, laboratory assessments will be performed, including whole blood viscosity, complete blood count (CBC), fibrinogen, globulins, lipid profile, ankle/toe brachial index, and pulse volume recording (PVR). Vital signs will also be assessed at each visit. At the end of 4 weeks treatment, all 3 groups will receive aspirin 81 mg for 2 weeks to reestablish baseline values. After the 2-week washout, the ticagrelor placebo and aspirin 81 mg treatment group (Group A) will be treated with aspirin 81 mg daily and ticagrelor; the aspirin 81 mg daily and ticagrelor treatment group (Group B) will be treated with ticagrelor monotherapy; and, the ticagrelor monotherapy group (Group C) will be treated with ticagrelor placebo and aspirin 81 mg daily for 4 weeks. After the end of 4 weeks treatment, again, all 3 groups will receive aspirin 81 mg for 2 more weeks to re-establish baselines. After this 2-week washout period, the third and final treatment will be for 4 weeks as follows: ticagrelor monotherapy for Group A, ticagrelor placebo and aspirin 81 mg for Group B, and ticagrelor with aspirin 81 mg for Group C. After randomization, the time-window beginning with Visit 1 and for

The 3 treatment groups will receive:

1. Group A: Aspirin 81 mg daily and ticagrelor placebo twice daily
2. Group B: Aspirin 81 mg daily and ticagrelor 90 mg twice daily
3. Group C: Aspirin placebo daily and ticagrelor 90 mg twice daily

Each treatment group will receive all 3 of the above treatments in this cross-over study.

Figure 1. Study Flow Sheet



[A] Laboratory Assessments: whole blood viscosity, CBC, fibrinogen, globulins, lipid profile, ankle/toe brachial index, pulse volume recording (PVR).
[B] Time Window is ± 7 days.
[C] ABI with exercise will be done at screening to identify subjects with claudication symptoms who may have resting ABIs > 0.85.

3.2 Rationale for study design, doses and control groups

A previous study comparing 120 patients having intermittent claudication with normal age-matched controls found blood viscosity was significantly higher among claudicants ($p < 0.001$) with the greatest difference in blood viscosity observed at lowest shears [3]. At high shear rates, patients with blood viscosity above 4.5 cP had mean claudication distance of 126 meters compared to 289 meters for patients with high-shear viscosity below that threshold. This report suggested the use of the term rheological claudication to describe approximately 25% of moderate to severe claudicants with hyperviscosity of blood having significantly worse prognoses.

In a random sample of 1,581 men and women 55 to 74 years of age with symptomatic or asymptomatic PAD, whole blood viscosity and fibrinogen were independently associated with peripheral arterial narrowing [4]. Plasma viscosity was also associated with claudication. The risk of claudication for patients in the upper quintile of plasma viscosity was 3.4 times greater than the risk for those in the lowest plasma viscosity quintile. The authors implicated blood rheological factors in the pathogenesis of lower limb ischemia in the general population.

The link between blood viscosity and ischemic heart disease events or strokes was reported in a study of a random population of 1,592 adults followed for a mean of 5 years: After adjustment for age and gender, both blood viscosity and hematocrit-corrected blood viscosity were higher in patients who experienced CVD events (myocardial infarction, angina pectoris, coronary revascularization or stroke) than in those who did not. The difference in blood viscosity between the two groups of patients was significant ($p=0.0003$) [5]. A number of outcome studies have demonstrated the risk of major CVD events increased with blood viscosity [6,7]. Stroke patients and those with stroke risk factors were shown to have chronically elevated blood viscosity relative to healthy controls [8].

A number of observational studies have reported increased blood viscosity in type 2 diabetics compared with nondiabetics. In an early clinical study comparing 16 diabetics with 16 age and gender-matched nondiabetic control subjects, mean blood viscosity at low shear rate was observed to be 26% higher in diabetics ($p<0.001$) [9]. A study of 38 male diabetics with and without retinopathy compared against 38 nondiabetics, matched for age and smoking habit, found low-shear blood viscosity levels were on average 13% higher in diabetics without retinopathy and 30% higher in those with retinopathy relative to control subjects [10]. These differences persisted after adjusting for hematocrit. A separate study of 64 diabetics and 61 matched nondiabetics reported similar results: elevated mean viscosity levels in diabetics compared with control subjects and the highest increases in diabetics with retinopathy or nephropathy [11].

Pharmacological therapies for reducing blood viscosity have been limited to clopidogrel [12], aspirin-dipyridamole [13] and in some studies pentoxifylline [14,15]. A reduction in blood viscosity has not been observed with either cilostazol [15] or ticlopidine [16]. In a double-blind, placebo-controlled study of 30 age and gender-matched patients with subclinical carotid or femoral atherosclerosis, clopidogrel was observed to reduce mean low-shear blood viscosity by 18% from baseline levels 3 weeks after administration ($p<0.01$) [12].

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion criteria

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

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

2. Subject is willing to comply with the requirements of the study protocol

3. Male or female ≥ 18 years of age

4. Type 2 diabetes mellitus

5. Symptomatic PAD

6. Ankle-brachial index ≤ 0.85 or calcified blood vessels with toe-brachial index ≤ 0.6 and/or abnormal post-exercise ankle-brachial index.7. Prior surgical or percutaneous intervention of the peripheral arteries ≥ -3 months with non-drug eluting stent placement and ≥12 months for those with drug-eluting stents previously with a residual stenoses of ≥ 50% in a non-dilated artery.

8. Subject has hypersensitivity or allergic reactions to clopidogrel

4.2 Exclusion criteria

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

1. Type I diabetes, poorly controlled diabetes (HbA1c ≥ ~~8.5 ± 0~~9.5%), newly diagnosed type 2 diabetes (within 6 months of randomization), or laboratory evidence of diabetes during screening (fasting serum glucose ≥ 126 mg/dL [7.0 mmol/L] or HbA1c ≥ 6.5%) without prior diagnosis of diabetes

2. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 180 mmHG or diastolic BP (DBP) > 100 mmHg

3. NYHA III or IV heart failure, or last known left ventricular ejection fraction (LVEF) ≤ 30%

4. Subject has a hypersensitivity or allergic reactions to ticagrelor

5. Subject has a hypersensitivity or allergic reactions to aspirin

6. Subject who has known sensitivity to any of the products or components to be administered during dosing or procedures

7. Need for chronic oral anticoagulation therapy (e.g. cilostazole) or chronic low-molecular-weight heparin or long-term treatment with fondaparinux

8. Planned revascularization (surgical or endovascular) in any vascular territory during the duration of the study

9. Planned amputation due to PAD within the duration of the study or amputation due to PAD within the last 30 days

10. Subjects who have suffered a stroke in the last 3 months

11. Dementia likely to jeopardize understanding of information pertinent to study conduct or compliance to study procedures

12. Subject has a history of severe liver disease (e.g. ascites and/or clinical signs of coagulopathy) or obstructive liver disease [(e.g. primary biliary cirrhosis or end-stage renal disease (eGFR $\leq$ 30 mL/min/m^2)]

13. A known bleeding diathesis, haemostatic or coagulation disorder, or systemic bleeding, whether resolved or ongoing

14. History of previous intracranial bleed at any time, gastrointestinal bleed within the past 6 months, or major surgery within the past 3 months of screening (if the surgical wound is judged to be associated with an increased risk of bleeding)

15. Considered at risk of hemorrhagic events

16. Subject who has not been on stable lipid lowering therapy in the last 3 months prior to LDL-C screening [e.g. red yeast rice, > 200mg/day niacin, or prescription lipid-regulating drugs (e.g. fibrates and derivatives, statins, ezetimibe) other than bile-acid sequestering resin, or stanols/plant stanols and stanol esters

17. Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosprorine, systemic steroids (e.g. IV, intramuscular [IM], or PO) (Note: hormone replacement therapy is permitted), Oral vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (e.g. Accutane); (Note: Vitamin A in a multivitamin preparation, as well as topical retinoid and retinol creams are permitted)

18. Initiation of prescription triglyceride lowering therapy (e.g. Lovaza) which is not stable within 6 weeks of screening

19. Subject has acute infection (e.g. bacterial, fungal) within the previous 6 weeks prior to screening (Note: subjects with a viral infection such as the common cold are not excluded)

20. Subject has anemia (hemoglobin $\leq$ 8.5 g/dL) that requires a potential blood transfusion within 6 weeks of screening

21. Subject has given blood or received a blood transfusion within the previous 3 months prior to screening

22. Subject has polycythemia vera or any hyperviscosity syndrome

23. Subjects with Waldenstrom's macroglobulinemia who have an increased risk of hyperviscosity syndrome

24. Female subject who has either (1) not used at least 1 highly effective method of contraception for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the subject is sterilized or postmenopausal. Menopause is defined as: 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old or 12 months of spontaneous and continuous amenorrhea with a follicle-stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy. Highly effective methods of birth control include: not having intercourse or using birth control methods that work at least 99% of the time when used correctly and include: birth control pills, shots, implants, or patches, intrauterine devices (IUDs), tubal ligation/occlusion, sexual activity with a male partner who has had a vasectomy, condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

25. Subject is pregnant or breast-feeding, or planning to become pregnant during treatment and/or within 15 weeks after the end of treatment

26. Subject who is likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (e.g. blood collection procedures to ensure subject safety to the best of the subject and investigator's knowledge

27. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outline above) that, in the opinion of the Investigator or Sponsor, if consulted, would pose a risk to subject safety or interferes with the study evaluation, procedures or completion (e.g. active malignancy other than squamous cell or basal cell skin cancer, use of strong or moderate CYP2C19 inhibitors, long-term concomitant treatment with non-steroidal anti-inflammatory drugs [NSAIDs])

28. Unreliability as a study participant based on the Investigator's (or designee's) knowledge of the subject (e.g. alcohol or other drug abuse, inability or unwillingness to adhere to the protocol, or psychosis)

29. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)

30. Family members or employees of the investigator or study centers involved in the study

5. STUDY CONDUCT

5.1 Restrictions during the study

- Patients must refrain from taking aspirin beyond the doses administered in the study.
- Patients must avoid giving blood or receiving a blood transfusion during the study duration

5.2 Subject enrollment and randomization

5.2.1 Procedures for randomization

Study participants will be randomized into 3 groups, and each group will receive each of 3 treatments in the cross-over study. Block randomization will be used to create groups which have equal and balanced sample sizes (i.e. for every block of 6 subjects, two will be enrolled to each arm of the study).

5.3 Procedures for handling subjects incorrectly enrolled

Subjects who are incorrectly enrolled or randomized will no longer qualify for the study and a replacement subject will be enrolled, if possible.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be a double-blind, double-dummy (both participants and clinicians), placebo controlled, cross-over study. Patient data will be coded and entered on a computer at the clinical site. All data will have password protection and controlled access. Drugs and placebos will also be coded to avoid bias when administering and taking the doses.

5.4.2 Methods for unblinding the study

At the conclusion of the study or if a serious adverse event is experienced, data will be decoded to reveal patient and therapy information.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Ticagrelor

ASA (Aspirin)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor	90 mg Tablet	AstraZeneca Pharmaceuticals LP
Chewable ASA (Aspirin)	81 mg Tablet	Any

5.5.2 Doses and treatment regimens

The 3 treatment groups will receive:

1. Group A: Aspirin 81 mg daily and ticagrelor placebo twice daily
2. Group B: Aspirin 81 mg daily and ticagrelor 90 mg twice daily
3. Group C: Aspirin placebo daily and ticagrelor 90 mg twice daily

Each treatment group will receive all 3 of the above treatments in this cross-over study.

5.5.3 Additional study drug

Not applicable

5.5.4 Labeling

Labeling for 4 treatments (aspirin 81 mg daily, aspirin placebo daily, ticagrelor 90 mg twice daily, and ticagrelor placebo twice daily) will be coded.

5.5.5 Storage

Ticagrelor will be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). ASA will be stored in a cool, dry place.

5.6 Concomitant and post-study treatment(s)

Not applicable.

5.7 Treatment compliance

All subjects will be counseled on the importance of taking their doses as directed. Each subject will be expected to document time and date of each dose in a daily dosing diary. Additionally, a pill count will be performed at each visit.

5.7.1 Accountability

The Principal Investigator undertakes to perform the study in accordance with GCP including requirements stated in the Code of Federal Regulations (e.g., 21 CFR – Part 312 Subpart D [Responsibilities of Sponsors and Investigators]).

The Principal Investigator is required to ensure compliance with respect to the visit schedule and procedures required by the protocol. The Principal Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to instructions provided.

The Sponsor of this study has responsibilities to Health Authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity, and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Medical Monitor and of his/her clinical research support team is to help the Investigator and the

Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters, or telephone calls by a representative of the monitoring team to review study progress, Principal Investigator and subject adherence to protocol requirements, and any emergent problems. During the monitoring visits, the following points will be scrutinized with the Principal Investigator: subject informed consent, subject recruitment and follow-up, study device allocation, subject compliance to the study procedures, study device accountability, concomitant therapy use, AE and SAE documentation and reporting, and quality of data. Sections of Case Report Forms (CRFs) may be collected on a per visit basis.

5.8 Discontinuation of investigational product

5.8.1 Procedures for discontinuation of a subject from investigational product

Subjects will be notified in person at the end of study visit, or under circumstances when this last visit has not been completed via telephone, or by certified mail upon determination that he or she will no longer receive the investigational product.

5.9 Withdrawal from study

Subjects MUST be withdrawn from the study for any of the following reasons:

- If the study appears to be medically harmful to the subject (e.g. an SAE).
- If the subject fails to follow the directions given by the Investigator or study staff required to continue in the study (e.g. personal reason).
- If it is discovered that the subject does not meet the study requirements.
- If the study is canceled by the study sponsor.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data; a black ballpoint pen should be used to ensure the clarity of reproduced copy of all CRFs.

Should a correction be made, the information to be modified must not be overwritten. The incorrect recording will have a single neat line drawn through it. The correct information will then be transcribed next to the previous value, along with the reason for the correction. The authorized person making the correction will then initial and date it.

6.2 Data collection at enrollment and follow-up

6.2.1 Enrollment procedures

Potential subjects will answer questions and these responses will be recorded on the CRF. Subjects will be asked if they are pregnant; pregnant subjects will not qualify for enrollment in this study. Qualifying subjects will be requested to enroll into the study. Subjects satisfying all inclusion criteria and without any reason for exclusion will be eligible for the study. Subjects not fulfilling the requirements are not eligible and will be replaced. The following data will be recorded on the subject's CRF: demographics, CVD risk factors (including smoker/non-smoker, hypertension, diet, physical activity), clinical history, vital signs, and medications. Those subjects who sign the informed consent and who pass the initial screening will be administered aspirin 81 mg by mouth once daily for 2 weeks.

After 2 weeks run-in treatment with aspirin 81 mg daily, patients will be randomized to one of 3 arms (ticagrelor placebo and aspirin 81 mg (Group A), ticagrelor and aspirin 81 mg (Group B), or ticagrelor monotherapy with aspirin placebo (Group C)) and treated for 4 weeks. Laboratory assessments will be performed, including whole blood viscosity, complete blood count (CBC), fibrinogen, globulins, lipid profile, ankle/toe brachial index, and pulse volume recording (PVR). Some of the laboratory samples will be stored in a -70°C freezer for future assessments and genetic testing. Vital signs will also be assessed at each visit.

Any adverse events (AEs) will be properly recorded on the CRF, and any Serious Adverse Events (SAEs) will be recorded on SAE forms (MEDWATCH 3500A Form) and the AE form of the CRF, and will be reported to the Sponsor. Any AE not resolved or not resolved with sequelae within thirty minutes after the scheduled blood draw will be followed until such resolution occurs, and this resolution will be noted on the CRF.

6.2.2 Follow-up procedures

The schedule for follow-up visits is described in Section 3.1. At each follow-up visit, laboratory assessments will be performed, including whole blood viscosity, complete blood count (CBC), fibrinogen, globulins, lipid profile, ankle/toe brachial index, pulse volume recording (PVR) and laser flow Doppler assessment. Some of the laboratory samples will be stored in a -70°C freezer for future assessments and genetic testing. Vital signs, medication adherence, medication safety, and medication efficacy will also be assessed at each visit.

6.3 Efficacy

6.3.1 Whole Blood Viscosity

Blood samples will be collected with a standard venipuncture. Approximately 3 cc of blood will be collected into an EDTA-containing vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and transported in a refrigerated shipment kit to Rheovector LLC (Camden, NJ) for viscosity testing. Blood viscosity will be measured using an automated scanning capillary tube viscometer across a physiologic range of shear rates of 1-1000 s^{-1} in increments of 0.1 s^{-1}. Blood viscosity levels at 5 s^{-1} will be reported as low-shear viscosity,

and blood viscosity measurements at 300 s^{-1} will be reported as high-shear viscosity. An additional 5 cc of blood will be collected for CBC testing.

Pulse volume recordings will be simultaneously obtained at the level of the ankle, metatarsal and toe bilaterally (Parks Flolab, Parks Medical Electronics, Aloha, OR) according to standard protocol

Continuous-wave doppler will be used to determine ankle-brachial indices or toe-brachial indices, and flow velocity profiles.

Perimed Inc's laser flow doppler system will be used to determine microcirculatory flow in a private research subject room. Perimed staff will train and certify study members. Only trained and certified study members listed on the protocol will be permitted to perform the procedure on study subjects.

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

6.4 Safety

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- 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 jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

6.4.3 Recording of adverse events

Time period for collection of adverse events

All adverse events, serious or non-serious, are to be recorded on the Adverse Event Form, which accompanies the CRF. This should be done as soon as possible but no longer than 24 hours after the event. The Investigator should specify the date of onset, seriousness, intensity, action taken on the study drug/device, corrective therapies given, outcome, date of resolution (if any), and his/her opinion as to whether the AE can be related to therapies or procedures involved in the study. The Investigator should also review with the monitor the suggested categories used for describing the relationship(s).

Follow-up of unresolved adverse events

Subjects withdrawn from the study due to any AE that is still ongoing will be followed at least until the outcome is determined, even if it implies that follow-up continues after the subject has left the study, and where appropriate until the end of the planned period of follow-up.

In the case of an SAE that is still ongoing, the subject must be followed-up until clinical recovery is complete or until progression has been stabilized. It may imply that this follow-up will continue after the subject has left the study.

As obtained, additional information will be noted on follow-up "Serious Adverse Event" Forms. As these are completed, the box marked "follow-up" is to be checked on these forms and the forms sent or faxed to the Medical Monitor.

The Sponsor is responsible for reporting faxed SAEs within required timelines promptly to the Health Authorities of different countries, as appropriate, except in those countries where it is the Investigator's legal responsibility.

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity, intensity, or changes in intensity of AE
- *Select the appropriate if needed: CTCAE grade/max CTAE grade/changes in CTCAE grade*
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- *Select the appropriate if needed:* AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- 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.

Adverse Events based on signs and symptoms

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

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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 (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of visual loss from diabetic retinopathy, diabetic and other ischemic ulcers, symptomatic hyperglycemia or hypoglycemia should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.4 Reporting of serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating 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

Investigative site must also 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.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

We will submit SAE reports to AstraZeneca using the MedDRA coding language.

6.4.5 Laboratory safety assessment

All laboratory equipment and devices will be regularly evaluated by the site and/or outside auditors for Good Clinical Practice and overall laboratory safety.

For the purpose of ensuring compliance with Good Clinical Practice and regulatory agency guidelines, it may be necessary for the Sponsor or a regulatory agency to conduct a site audit or an inspection.

For blood volume see Section 7.17.1.

6.5 Physical examination

The physicians at the three sites will perform a general physical examination of all major organ systems.

6.5.1 ECG

6.5.1.1 Resting 12-lead ECG

A 12-lead resting electrocardiogram will be performed at screening and end of trial.

6.5.1.2 Real time display (telemetry)

Not applicable.

6.5.2 Vital signs

Vital signs will be obtained in the sitting position after five (5) minutes of rest, prior to the viscosity test, and recorded on the CRF.

6.5.2.1 Pulse and blood pressure

Radial pulse will be measured as beats/minute. The quality of the pulse will also be noted. Systolic and diastolic blood pressure will be measured as mmHg.

6.5.2.2 Body temperature

Body temperature will be measured as °F.

6.5.3 Other safety assessments

Pulse volume recordings will be simultaneously obtained at the level of the ankle, metatarsal and toe bilaterally (Parks Flolab, Parks Medical Electronics, Aloha, OR) according to standard protocol

Continuous-wave Doppler will be used to determine ankle-brachial indices as well as toe-brachial indices.

Perimed, Incs laser doppler monitoring system (PeriFlux System 5000, Perimed AB, Sweden) will measure the total local microcirculatory blood perfusion including the perfusion in capillaries, arterioles, venules and shunting vessels. The technique is based on the emission of a beam of laser light carried by a fiber-optic probe. This probe will be connected to a computer system where we will be able to obtain the measurements. This assessment will take only 2-6 min and will not involve the use of any radiation. The measurements of the flow will be performed with and without Valsalva maneuvers.

Perimed's Periflux system has been used in other clinical trials as evidenced in published scientific journals.

6.6 Patient reported outcomes (PRO)

Not applicable.

6.6.1 PRO method or questionnaire

MedDRA.

6.7 Pharmacokinetics

Not applicable.

6.7.1 Collection of samples

Blood samples will be collected with a standard venipuncture. Approximately 3 cc of blood will be collected into an EDTA containing vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and utilized within the Hemathix SCV-200 automated scanning capillary tube viscometer. An additional 20 cc of blood will be collected for CBC and other lab testing.

6.7.2 Determination of drug concentration

Not applicable.

6.8 Pharmacodynamics

Not applicable.

6.8.1 Collection of pharmacodynamic markers

Not applicable.

6.9 Pharmacogenetics

6.9.1 Collection of pharmacogenetic samples

6.10 Some of the laboratory samples will be stored in a -70°C freezer for future assessments and genetic testing if consented by the subject.Health economics

Not applicable.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

Blood samples will be collected with a standard venipuncture. Approximately 3 cc of blood will be collected into an EDTA containing vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and utilized within the Hemathix SCV-200 automated scanning capillary tube viscometer. An additional 20 cc of blood will be collected for CBC testing, fibrinogen, serum chemistry and lipid profiles. A serum pregnancy test will be performed on all women who agree to participate in the trial.

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Not applicable.

7.2.2 Pharmacogenetic samples

Some of the laboratory samples will be stored in a -70°C freezer for future assessments and genetic testing if consented by the subject. For subjects that do not consent for pharmacogenetic, samplease would not be collected and/or will be destroyed immediately.

7.3 Labeling and shipment of biohazard samples

Three preprinted labels containing the Subject ID number will be prepared for each subject. The labels will be affixed to the blood specimen tubes for each test as well as each subject's CRF. Blood will be sent to a designated laboratory facility.

7.4 Chain of custody of biological samples

The chain of custody for biological samples follows from the study coordinator and local principal investigator, to the central laboratory facility for blood viscosity or to the site medical center laboratory for all other laboratory assessments.

7.5 Withdrawal of informed consent for donated biological samples

In the event that a subject withdraws his or her informed consent for donated biological samples, all of his or her samples will be disposed of and excluded from further study.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be conducted in compliance with the protocol and GCP. In reference to other applicable regulatory requirements, the automated scanning capillary viscometer is an investigational device that requires a minimally invasive sampling procedure that presents no significant risk. It does not by design or intention introduce energy into a subject, and it is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established product or procedure. In addition, the blood sample required for testing in the device will be collected with a standard venipuncture, which is an approved FDA procedure (the blood is not returned to the subject’s body). The device is considered to be exempt from IDE regulation in accordance with the provisionals specified in 21 CFR 812.2 and 812.5

8.2 Ethics and regulatory review

The Principal Investigator must submit this protocol to an Ethics Review Committee or a similar body (IRB, CCPPRB, etc.), and he/she is required to forward a copy of the written approval/advice signed by the Chairman to the Sponsor.

On the approval/advice sheet, the study (title, protocol number, and version), the documents studied (protocol, informed consent material, advertisement, when applicable), and the date of the review should be clearly stated.

Study device supplies will not be released, and the study will not start until a copy of this written approval/advice has been received by the Sponsor.

Complementary information and/or requirements will be described in an appendix, where applicable.

8.3 Informed consent

It is the responsibility of the Principal Investigator to obtain informed consent in compliance with national requirements from each subject prior to entering the study or, where relevant, prior to evaluating the subject's suitability for the study.

The informed consent document used by the Principal Investigator for obtaining subject's informed consent must be reviewed and approved by the Sponsor prior to Ethics Review committee or similar body (IRB, CCPPRB, etc.) submission.

Specific national requirements or specific conditions associated to the study procedures will be described in an appendix, where applicable.

8.4 Changes to the protocol and informed consent form

It is specified that the appendices attached and referred to in the main text of this protocol form an integral part of the protocol.

No change or amendment to this protocol may be made by the Principal Investigator or by the Sponsor after the protocol has been agreed to and signed by both parties unless such change or amendment has been fully discussed and agreed upon by the Principal Investigator and the Sponsor. Any changes so agreed upon will be recorded in writing, and the written amendment will be signed by both the Principal Investigator and Sponsor. The signed amendment will then be appended to this protocol.

Approval/advice of amendments by the Ethics Review Committee or similar body (IRB, CCPPRB, etc.) is then required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full Ethics Review Committee approval/advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, such approval/advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The Principal Investigator must receive Ethics Review Committee approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the CRFs, if required, will be incorporated into the amendment.

Prior to initiating the change, the protocol amendment must be submitted to the Regulatory Agencies, where applicable, except under emergency conditions.

8.5 Audits and inspections

By signing this protocol, the Principal Investigator agrees to allow Sponsor Clinical Research/Quality Assurance auditors and regulatory agencies to have direct access to his/her study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in the Case Report Forms, review of documentation required to be maintained, and checks on drug/device accountability.

9. STUDY MANAGEMENT

9.1 Training of study site personnel

Training of study site personnel is the responsibility of the PI. Training of staff personnel in all amendments should be documented in the Regulatory Binder.

9.2 Monitoring of the study

9.2.1 Source data

According to the guidelines on GCP, the monitor has to check the CRF entries against the source documents. The consent form will include a statement by which the subjects allow the Sponsor's duly authorized personnel (Study Monitoring team) to have direct access to source data which supports data on the CRFs (e.g. subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

9.3 Study timetable and end of study

See section 3.1 for complete study timetable and flow chart. The study will conclude at week 16 after the final collection of patient data and laboratory assessments.

10. DATA MANAGEMENT

All local legal requirements regarding the protection of personal data will be adhered to. Patient data will be coded with a subject ID.

All subject data is confidential, but may be subject to review by authorized representatives of the sponsor, independent auditors, IRB, and/or regulatory authorities.

All data will be secured in secure locked cabinets, and on a secure, password-protected server.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

Blood samples will be collected with a standard venipuncture. Approximately 3 cc of blood will be collected into an EDTA containing vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and utilized within the Hemathix SCV-200 automated scanning capillary tube viscometer. An additional 5 cc of blood will be collected for CBC testing.

Pulse volume recordings will be simultaneously obtained at the level of the ankle, metatarsal and toe bilaterally (Parks Flolab, Parks Medical Electronics, Aloha, OR) according to standard protocol

Continuous-wave Doppler will be used to determine ankle-brachial indices as well as toe-brachial indices.

11.2 Calculation or derivation of safety variable(s)

Not applicable.

11.2.1 Other significant adverse events (OAE)

Not applicable.

11.3 Calculation or derivation of patient reported outcome variables

Not applicable.

11.4 Calculation or derivation of pharmacokinetic variables

Not applicable.

11.5 Calculation or derivation of pharmacodynamic variable(s)

Not applicable.

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Not applicable.

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables

Not applicable.

11.6 Calculation or derivation of pharmacogenetic variables

Not applicable.

11.7 Calculation or derivation of health economic variables

Not applicable.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

The data will be analyzed within the crossover design framework using repeated measures ANOVA. The analyses of treatment effect, period effect, and sequence effect will be performed at the 0.05 significance level.

12.1.1 Efficacy analysis set

For the first primary aim, a pre-planned contrast statement (proc mixed) will be used to compare the pooled effect of aspirin-ticagrelor with aspirin. Similarly, for the second primary aim, a contrast statement will be used to compare the pooled effect of ticagrelor monotherapy with aspirin. A one-tailed hypothesis test will be used for each contrast, and a Bonferroni correction will be used to control family wise error rate; a one-tailed significance level of 0.025 will be used for both contrasts. The above contrasts shall act effectively as a paired t-test on the dependent variable blood viscosity.

For the first secondary aim, an effect size will be calculated to estimate the standardized difference between ticagrelor monotherapy and combination aspirin-ticagrelor. Low-dose aspirin was previously reported to have no significant effect on blood viscosity. The present study is powered to detect differences between ticagrelor and low-dose aspirin—not between ticagrelor monotherapy and combination aspirin-ticagrelor. An effect size corresponding to a dependent t-test will be calculated to determine the practical magnitude of the difference in blood viscosity measures between the two ticagrelor arms of the study.

12.1.2 Safety analysis set

Not applicable.

12.2 Methods of statistical analyses

All statistical analyses will be performed using SAS (Statistical Analyses System, Cary, NC). Our statistical considerations assume that there is no carryover effect between treatments. In order to verify this assumption, dependent t-tests will be conducted to compare day 1 and week 6 measures of blood viscosity, and dependent t-tests will be conducted to compare day 1 and week 12 measures for blood viscosity.

12.2.1 Interim analyses

Not applicable.

12.3 Determination of sample size

The scanning capillary viscometer that will be used in the proposed study was employed in an earlier study of 47 patients with hyperhomocysteinemia in addition to stable CVD or high CVD risk factors based on a Framingham score of >20% [13]. In this prior CVD population, mean blood viscosity levels at a low shear rate of 5 s^{-1} were reported to be 9.98 ± 2.42 cP in the control group at baseline. A standard deviation of 2.42 cP for low-shear (5 s^{-1}) blood viscosity was used throughout our sample size calculations. Separately, treatment by clopidogrel 75 mg daily for 3 weeks was reported to reduce viscosity levels by 0.6 cP and 5.0 cP at shear rates of 94.5 s^{-1} and 0.94 s^{-1}, respectively [12]. Using this data, blood viscosity reduction of 2.0 cP by clopidogrel was interpolated for a shear rate of 5 s^{-1}. The present cross-over design study is powered to detect a 2.0 cP difference in low-shear blood viscosity at a shear rate of 5 s^{-1}, relative to aspirin 81 mg, with 90% power using a type I error rate of 5%. Combination aspirin-ticagrelor and low-dose aspirin control will be compared, and separately, ticagrelor monotherapy and low-dose aspirin control will be compared. This requires 72 patients (24 patients in each of 3 groups). Accounting for dropout, we will randomize 90 patients, or 30 patients in each of 3 arms. The effects of combination aspirin-ticagrelor and ticagrelor monotherapy will also be compared as a secondary aim.

12.4 Data monitoring committee

Unless specifically requested by the IRBs at the clinical sites, we will not convene a DMC due to the short-term nature of the trial. If a formal DMC is required, the appropriate costs for the physician's time will be included in a revised budget.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Overdose

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 **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 works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

13.2 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.2.1 Maternal exposure

Not applicable.

13.2.1.1 Paternal exposure

Not applicable.

14. LIST OF REFERENCES

1. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.

2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348:1329-39.

3. Dormandy JA, Hoare E, Postlethwaite J. Importance of blood viscosity. Rheological claudication. Proc R Soc Med 1974; 67:446-7.

4. Lowe GD, Fowkes FG, Dawes J, et al. Blood viscosity, fibrinogen, and activation of coagulation and leukocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. Circulation 1993; 87:1915-20.

5. Lowe GD, Lee AJ, Rumley A, et al. Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study. Br J Haematol 1997; 96:168-73.

6. Danesh J, Collins R, Peto R, Lowe GD. Haematocrit, viscosity, erythrocyte sedimentation rate: meta-analyses of prospective studies of coronary heart disease. Eur Heart J 2000; 21:515-520.

7. Ciuffetti G, Schillaci G, Lombardini, et al. Prognostic impact of low-shear whole blood viscosity in hypertensive men. Eur J Clin Invest 2005; 35:93-98.

8. Coull BM, Beamer N, et al. Chronic blood hyperviscosity in subjects with acute stroke, transient ischemic attack, and risk factors for stroke. Stroke 1991; 22:162-8.

9. Skovborg F, Nielsen AV, Schlichtkrull J, Ditzel J. Blood-viscosity in diabetic patients. Lancet 1966; 1(7429):129-31.

10. Lowe GD, Lowe JM, Drummond MM, et al. Blood viscosity in young male diabetics with and without retinopathy. Diabetologia 1980; 18:359-63.

11. Barnes AJ, Locke P, Scudder PR, Dormandy TL, Dormandy JA, Slack J. Is hyperviscosity a treatable component of diabetic microcirculatory disease? Lancet 1977; 2:789-91.

12. Ciuffetti, G., et al., Clopidogrel: Hemorheological effects in subjects with subclinical atherosclerosis. Clin Hemorheol Microcirc 2001; 25:31-9.

13. Rosenson RS. Treatment with aspirin and dipyridamole is more effective than aspirin in reducing low shear blood viscosity. Microcirculation 2008;15:615-20.

14. Muravyov AV, Bulaeva SV, Tikhomirova IA, Zamishlayev AV, Uzikova EV, Miloradov MJ. Macro- and microrheological parameters of blood in patients with cerebral and peripheral atherosclerosis: the molecular change mechanisms after pentoxifylline treatment. Clin Hemorheol Microcirc. 2011;49:431-9.

15. Dawson DL, Zheng Q, Worthy SA, Charles B, Bradley DV Jr. Failure of pentoxyifylline or cilostazole to improve blood and plasma viscosity, fibrinogen and erythorcyte deforability in claudication. Angiology. 2002;53:509-20.

16. Fagher B, Persson S, Persson G, Larsson H. Blood viscosity during long-term treatment with ticlopidine in patients with intermittent claudication. A double-blind study. Angiology. 1993 4:300-6.

17. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline) a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Journal of the American College of Cardiology 2011; 58:2020-45.

18. Gaglia MA, Waksman R. Overview of the 2010 food and drug administration cardiovascular and renal drugs advisory committee meeting regarding ticagrelor. Circulation 2011; 123:451-6.