Drug Substance	Brilinta//Ticagrelor
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Compare the efficacy of different antiplatelet therapy strategy after Coronary Artery Bypass Graft Surgery

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Graft
ECG	Electrocardiogram
MSCTA	Multislice computed tomography angiography
OPCAB	Off-pump Coronary Artery Bypass
UCG	Ultrasonic Cardiogram
CCS	Canadian Cardiovascular Society
PLATO	Platelet inhibition and patient Outcomes trial
AE	Adverse Event
SAE	Serious Adverse Event
IEC	Independent Ethics Committee
PI	Principal Investigator
TIMI	Thrombolysis in Myocardial Infarction

1. INTRODUCTION

1.1 Background

For 30 years, antiplatelet therapy has been the gold standard for preventing saphenous vein graft closure after CABG.[1] Aspirin is recognized as the standard of care and is generally continued indefinitely given its benefit in preventing subsequent clinical events.[2,3] But 2010 Canadian guideline[4] and 2012 Society of Thoracic Surgeons guideline[5] recommended that in patients undergoing CABG after ACS, dual antiplatelet drugs should be restarted and that may have secondary benefit of increasing early vein graft patency. Hence, different antiplatelet therapy strategy after CABG is still in controversy.

However, as many as 50% of patients do not have adequate response to aspirin on the first postoperative day after cardiac procedures, and this percentage increases in the first week after operation, especially for off-pump procedures.[6-8] Interestingly, the addition of clopidogrel did not seem to alter this nonresponse to aspirin. The clinical consequences of this lack of response remain uncertain, but evidence suggests lack of response to aspirin correlates with early vein graft closure after CABG and with recurrent cardiac events.[9,10]

In patients with high residual platelet reactivity after the usual doses of clopidogrel, the novel antiplatelet agents are more effective at reducing platelet reactivity compared with increasing dose of clopidogrel.[11] In the PLATO[12] trial, ticagrelor, a novel reversible inhibitor of the P2Y12 receptor, in addition to aspirin significantly reduced cardiovascular events in patients with ACS as compared to aspirin plus clopidogrel. The CABG substudy of the PLATO trial[13] showed ticagrelor compared with clopidogrel was associated with a substantial reduction in total and CV mortality without excess risk of CABG-related bleeding.

1.2 Research hypothesis

This study is designed to show the superiority of ticagrelor and ticagrelor plus aspirin as compared with aspirin monotherapy respectively for the 1-year primary efficacy end point of vein graft patency.

1.3 Rationale for conducting this study

For the study rationale, four recent published guidelines on CABG stated different antiplatelet therapy strategy for post-CABG is still in controversy. As 2010 ESC guideline on myocardial revascularization[14] and 2011 ACCF/AHA Guideline for CABG[15] recommended, aspirin monotherapy should be given to reduce the occurrence of vein graft closure and adverse cardiovascular events (Class I recommendation), but dual antiplatelet therapy is recommended (Class I) in 2010 Canadian guideline[4] and 2012 society of thoracic surgeons guideline.[5]

PLATO-CABG subgroup[13] analysis showed that combination ticagrelor with aspirin is effective in this population, but it is still not clear which one will be more benefit for from dual antiplatelet or monotherapy as current controversy in patients receiving clopidogrel.

A systematically review[16] showed that clopidogrel treatment alone demonstrate inferior with combination clopidogrel with aspirin in CABG patients.

Arterial graft patency rates are high even in the absence of antiplatelet therapy, the administration of antiplatelet therapy has not shown an improvement.[15] In previous published literatures and datas in our center , compared with artery graft, vein graft patency rate is lower. Meanwhile, short-term(one year) stenosis or closure of vein graft is the main factor for thrombosis.[17-18] So vein graft patency is an objective index for evaluating the effect of CABG postoperative.

1.4 Benefit/risk and ethical assessment

The Prescription Information for ticagrelor contains the information supporting the overall risk/benefit assessment of the investigational agent and is available as a reference for investigators. It contains a summary of all the relevant pharmaceutical, nonclinical and clinical findings with ticagrelor.

Patients enrolled in this study will be treated with ticagrelor. Participation will entail recording of medical information about the patient in a confidential manner. Patient care will not be altered by participation. Ticagrelor will be provided to the subjects for free. The risks to patients include bleeding and dyspnoea, which are believed to be adequately handled in the clinical situation. The study will be approved by the local research ethics committee.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study will be to evaluate whether, as compared with aspirin monotherapy, ticagrelor plus aspirin and ticagrelor monotherapy could increase saphenous vein graft patency at 12 months after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography (CAG).

2.2 Secondary objectives

1) Saphenous vein graft patency at 7th day after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography(CAG).

2) Time to first event of major adverse cardiovascular event (MACE), composite of CV death, myocardial infarction or stroke (ischaemic or unknown etiology).

3）Rate of freedom from angina by questionnaire according to CCS classification at 12 months.

4） Rate of post-operative atrial fibrillation within 7 days post CABG.

2.3 Safety objective

1) To compared with aspirin monotherapy, the major bleeding risk of ticagrelor plus aspirin and ticagrelor monotherapy according to Thrombolysis in Myocardial Infarction (TIMI) criteria.

2) Other advers events (AEs) during the study

2.4 Exploratory objectives

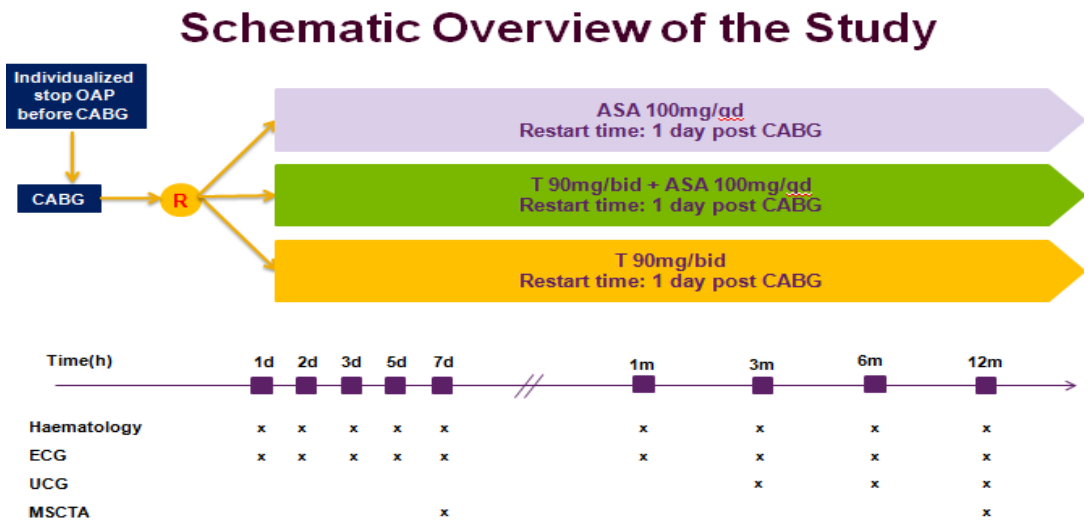
None.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

The study population will include all patients undergoing elective CABG. Consent and randomization will occur before surgery. Total 500 patients undergoing elective CABG will be randomly assigned into three groups with 1:1:1 ratio(167 patients per group) in this open-label study. All the enrolled patients will stop oral antiplatlet drugs according to local protocol before the surgery. Within the first 24 hours after surgery, study medication should be restarted and continued for 12 months. Arm A will restart oral antiplatelet drugs by giving aspirin 100mg qd, Arm B will also restart oral antiplatelet drugs by giving ticagrelor 90mg bid plus aspirin 100mg qd and Arm C will also restart oral antiplatelet drugs by giving ticagrelor 90mg bid. Treatment will continue for 12 months, at which time patients will undergo a multislice computed tomography angiography to assess vein graft patency.

Figure 1: Schematic Overview of the Study



3.2 Rationale for study design, doses and control groups

According to the previous CABG guideline, standard antiplatelet treatment strategy, ASA monotherapy should be taken lifelong after the operation. But 2012 society of thoracic surgeons guideline[5] updated that dual antiplatelet therapy are recommended for ACS population after CABG (Ia). On the other hand, PLATO-CABG substudy showed compared with clopidogrel, ticagrelor was associated with a substantial reduction in total and CV mortality without excess risk of CABG-related bleeding. Meanwhile, even with routine aspirin use after CABG, 10-20% of vein grafts occlude within 1 year after surgery, placing these patients at high risk for future myocardial events. Ticagrelor has a more consistent and pronounced platelet inhibition than clopidogrel, and may substantially improve graft patency following CABG compared to aspirin. We therefore propose this pilot study to compare 1-year vein graft patency among patients treated after CABG with ticagrelor plus aspirin or ticagrelor monotherapy, to those treated with aspirin monotherapy.

Based on the protocol and final data of PLATO study, the doses of ticagrelor and aspirin are recommended as below:

Ticagrelor: 90mg twice daily for 12 months

Aspirin: 100mg daily for 12 months

4. SUBJECT SELECTION CRITERIA

Screening for eligible subjects will be performed before CABG.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1 Inclusion criteria

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

1. Patients able to provide written informed consent

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

3. Female and male patients aged 18-80 years

4. Indication for CABG surgery:

- coronary three vessel disease, or
- left main stenosis, or

- two vessel disease with impaired left ventricular function

4.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Cardiogenic shock, haemodynamic instablity
2. Need for urgent revascularization within 5 days from presentation
3. Single vessel disease
4. Two vessel disease with normal LV function (≥ 50%)
5. Need for concomitant other cardiac surgery (e.g. valve replacement)
6. Need for dual antiplatelet treatment for the patients undergoing CABG after ACS
7. Contraindication for aspirin and ticagrelor use(e.g. known allergy)
8. History of bleeding diathesis within 3 months prior presentation
9. History of significant GI bleed within 1 year prior presentation
10. History of peptic ulcer without GI bleeding in past 3 years
11. History of intracranial hemorrhage
12. History of moderate to severe liver impairment
13. Patient requires dialysis
14. Patient with an increased risk of bradycardic events (as patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope)
15. Need VKA therapy after bypass surgery eg. persistent atrial fibrillation, mechanical valves
16. Known, clinically important thrombocytopenia(i.e. < $100*10^9$/L)
17. Known, clinically important anaemia (i.e. <100g/L)
18. Participation in another investigational drug or device study in the last 30 days
19. Pregnancy or lactation(for premenopausal women 2 methods of reliable contraception, one of which must barrier method, are required)
20. Concomitant oral or intravenous therapy with strong CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers which cannot be

stopped for the course of the study (strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 litre daily of grapefruit juice. Substrats with narrow therapeutic index: cyclosporine, quinidine. Strong inducers: rifampin, phenytoin, carbamazepine.)

21. Any other condition such as active cancer

22. Life expectancy less than 12 months that may result in protocol non-compliance or a risk for being lost to follow up

23. Indication for major surgery(e.g. cancer treatment, carotid surgery, cerebral surgery, major vascular surgery)

5. STUDY CONDUCT

5.1 Restrictions during the study

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

Restrictions regarding concomitant medications are described in Section 4.2

5.2 Subject enrollment and randomization

5.2.1 Subject enrollment

Patients who are ready for CABG and ticagrelor and aspirin treatment and eligible for the study will be included after obtaining the informed consent form.

5.2.2 Procedures for randomization

Patient eligibility will be established before treatment randomization. Patients will be enrolled/randomized strictly sequentially, as patients become eligible for enrolment/randomization. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

After providing informed consent, patients who are consistent with the inclusion and exclusion criteria will be randomly assigned to one of the three treatment groups. The randomization will be performed by a computer equally for the three treatment regimens. Each centre will be provided with sealed treatment code envelopes corresponding to a list of patient randomization numbers. Randomization numbers will be assigned strictly sequentially as subjects become eligible for randomization. When a subject is allocated to a specified randomization number, the corresponding code envelope will be opened to identify the allocated treatment regimen.

5.3 Procedures for handling subjects incorrectly enrolled

Every attempt will be made to detect the reason for incorrectly enrollment. Removal from the trial will be determined by the principal investigator (PI), and the reasons should be documented in the case report form (CRF).

5.4 Blinding and procedures for unblinding the study

This is an open-label study, so blinding is not applicable.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Ticagrelor is the study drug and aspirin is the comparator. Ticagrelor will be provided by AstraZeneca for free to subjects. The identity of those drugs is provided in the below table.
Table 1: Identity of investigational products

Investigational product	Physical description	Dosage form and strength	Manufacturer
Aspirin(Bayaspirin)	White, enteric-coated tablets	each tablet contains 100 mg acetylsalicylic acid	Bayer
Ticargrelor(Brilinta)	Round, biconvex, yellow, film-coated tablets marked with '90' above 'T' on one side and plain on the other	each tablet contains 90mg ticagrelor	AstraZeneca

5.5.2 Doses and treatment regimens

Arm A: Aspirin 100mg qd for 12 months

Arm B: Ticargrelor 90mg bid plus Aspirin 100mg qd for 12 months

Arm C: Ticargrelor 90mg bid for 12 months

5.5.3 Additional study drug

Not applicable.

5.5.4 Labeling

The labels of study drugs will accord with applicable relevant provisions and regulations.

5.5.5 Storage

Ticagrelor: Store at 25℃ (77℉); excursions permitted to 15° -30℃ (59° - 86℉).

Aspirin: Store at 25℃ (77℉); excursions permitte d to 15°–30℃ (59° –86℉) .

5.6 Concomitant and post-study treatment(s)

Concomitant treatment with oral anticoagulant drugs is not permitted during the study. If treatment with oral anticoagulant drugs is considered essential during the study, study medication must be discontinued but may be resumed if anticoagulant therapy can be stopped. In this study, the total treatment days of antiplatelet/anticoagulation therapy's temporary adjustment can not exceed 60.

Treatment with GPIIb/IIIa receptor antagonists is allowed pre-study.

Patients will receive concomitant therapies in three groups as recommended by the current American College of Cardiology / American Heart Association guidelines. This will include smoking cessation counseling and the administration of beta blockers, angiotensin converting enzyme inhibitors, and lipid-lowering medications as indicated. The usage of ticagrelor or clopidogrel after the end of the study will be determined by the doctors according to the clinical practice and disease conditions.

5.7 Treatment compliance

Dosage and administration of medications will be verified by review of medical record.

5.7.1 Accountability

Ticagrelor will be donated by AstraZeneca, while aspirin will be purchased by subjects themselves. The investigator is responsible for ensuring that all study drug of ticagrelor received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject, must be documented on the drug accountability form. Subjects or their legally acceptable representatives must be instructed to return all original containers, whether empty or containing study drug.

5.8 Discontinuation of investigational product

5.8.1 Procedures for discontinuation of a subject from investigational product

Patients have the right to discontinue the study drug at any time without the need to justify the decision. The investigator has the right to discontinue patients from the study drug for non-compliance, administrative or other reasons.

Patients should discontinue the study drug prior to completion if any of the following criteria are observed:

- Major protocol violation assessed by the PI (including poor compliance, inconsistency with the inclusion and exclusion criteria, etc.).

- In light of safety issues, it is no longer proper for the patient to participate in the trial because of the occurrence of AEs.
- Withdrawal required by the patient. Patient refuses to participate or continue to participate in the trial.
- Pregnancy.

5.9 Withdrawal from study

It is understood that an excessive rate of withdrawals can render the study results uninterpretable; therefore unnecessary discontinuation of patients should be avoided. The sponsor reserves the right to terminate a patient from the trial for non-adherence.

Criteria of removal of patients from the trial:

- Discontinuation of study drug.
- Loss to follow-up.
- Death.

Every attempt will be made to detect the reason for withdrawal from the trial, e.g. AEs, lack of efficacy, removal from the trial determined by the investigator, other reasons which should be documented in the CRF. AEs should be assessed, determined and followed up by the investigators. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject discontinues treatment before the end of the study, end-of-treatment assessments should be obtained.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The investigator will ensure that data are recorded on the paper Case Report Forms (CRF) as specified in the study protocol and in accordance with the instructions provided. We will record age, gender, medical history, diagnosis leading to CABG and also record key laboratory results including hematology, biochemistry, biomarker, coagulation, etc.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed paper CRF. A copy of the completed paper CRF will be archived at the study site.

6.2 Data collection at enrolment and follow-up

All data will be collected after the patients providing informed consent and before the end of MSCTA examination. Refer to the Time and Events Schedule below for an overview of key

procedures performed during the study, including the evaluation frequency and timing of efficacy, safety, and other indices.

Table 2: Time and Events Schedule

Phase	**Baseline/ Screening[4]**	**Treatment (Day 1-Day 360)**								
						Discharge[2]				**Endpoint[3]**
Treatment Day[1]		**D1**	**D2**	**D3**	**D5 ±1**	**D9 ±2**	**D30 ±7**	**D90 ±7**	**D180 ±14**	**D360 ±14**
Visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Informed Consent Form[5]	X									
Medical History	X									
Vital Signs	X									
Physical Examination	X									
Concomitant medications	X									
Hematology	X									
Coagulation	X									
Biochemistry	X									
Inclusion/Exclusion Criteria		X								
Randomization		X								
Ticagrelor 90mg bid		X	X	X	X	X	X	X	X	X
Aspirin 100mg qd		X	X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X	X

UCG	X							X	X	X
MSCTA[6]						X				X
Pregnancy Test		X								
Bleeding Events		X	X	X	X	X	X	X	X	X
AEs[7]		X	X	X	X	X	X	X	X	X

NOTE:
1. CAGB procedure will be operated on Day 0
2. Discharge examination on Day 9±2 may be optional according to each center's routine care.
3. Subject who prematurely terminate treatment for any reason have to complete all the tests listed in the endpoint column. Follow-up duration can be 12 months
4. Investigators must test all the screening results before study drug administration.
5. Informed consent form must be obtained before any study -related procedure.
6. MSCTA: Multislice Computed Tomography Angiography
7. AEs recording began from the signing of informed consent throughout the study until and including the last visit.

6.2.1 Enrollment procedures

Patients undergoing CABG procedures will be pre-screened for eligibility in the study. Inclusion and exclusion criteria will be reviewed. Once a patient is deemed eligible for the study, the patient will be invited to participate. At this period, obtain the following baseline information:

1. Medical history;

2. Perform comprehensive physical examination [hematology, biochemistry, biomarker, coagulation, ECG, chest radiography, color Doppler ultrasound (carotid artery /arteria cruralis vessel), lung function (if necessary), chest CT (if necessary), head CT (if necessary), cardiac MRI (if necessary) , myocardium nuclide test (if necssary)] EuroScore assessment according to the patient medical history and preoperative evaluation data];

3. Combine Syntax score with EuroScore to do the global risk classification (GRC).

4. Record concomitant medications;

5. Pregnancy test in women;

6. Monitor adverse events.

Eligible patients are randomly assigned to one of the following open-label treatment regimens at a ratio of 1:1:1.

Subjects are randomized to one of the three treatment groups: "Aspirin" group (Arm A) or "Ticagrelor+Aspirin" group (Arm B) or "Ticagrelor" group (Arm C)

6.2.2 Follow-up procedures

Visit 1 (the 1st day after the operation):

Blood routine examination, myocardial injury biomarker, and ECG will be conducted.

From visit 2 (the 2nd day after the operation) to visit 4 (the 5th±1 day after the operation):

Blood routine examination, myocardial injury biomarker will be conducted

24 hours ECG monitoring will be reviewed daily to exam and record the incidence of atrial fibrillation/supraventricular tachycardia

Visit 5 (the 9th±2 day after operation):

MSCTA or CAG will be conducted to assess the saphenous vein graft patency according to Fitzgibbon Class

Questionnaire survey will be taken according to CCS

Review the data of hematology and imaging exams during hospitalization

From visit 6 (the 30th±7 day after operation):

Questionnaire survey will be taken according to CCS

Hamatology examination、ECG will be conducted

From visit 7 (the 90th±7 day after operation) to visit 8 (the 180th±14 day after operation):

Questionnaire survey will be taken according to CCS

Hamatology examination、ECG、UCG will be conducted

Visit 9 (the 360th±14 day after operation):

Questionnaire survey will be taken according to CCS

Hamatology examination、ECG、UCG will be conducted

MSCTA or CAG will be conducted to assess the saphenous vein graft patency according to Fitzgibbon Class.

6.3 Efficacy

6.3.1 Efficacy variable

1. Primary efficacy endpoint:

Angiographic vein graft patency by MSCTA or CAG at 12 months after CABG.

The patency of grafts will be defined according to the Fitzgibbon Standards, and they will be finally judged by IDRC（Refer to 12.4.1）

2. Secondary efficacy endpoint:

1) Angiographic vein graft patency by MSCTA or CAG at 7th day after CABG.

The patency of grafts will be defined according to the Fitzgibbon Standards, and they will be finally judged by IDRC（Refer to 12.4.1）

2) Time to first event of MACE, composite of CV death, myocardial infarction or stroke (ischaemic or unknown etiology) at 12 months after CABG.

The MACE will be defined according to <2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials>, and they will be finally judged by CEC（Refer to 12.4.2）

3) Rate of freedom from angina by questionnaire according to CCS classification at 12 months after CABG.

4) Rate of post-operative atrial fibrillation within 7 days after CABG.

6.4 Safety

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

1. Bleeding events:

Incidence of bleeding events, classified by the following TIMI criteria.

Table 3: Criteria of Bleeding Events

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

	○ Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL Requiring medical attention ○ Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above ○ Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) ○ Leading to or prolonging hospitalization ○ Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging) Minimal ○ Any overt bleeding event that does not meet the criteria above Bleeding in the setting of CABG ○ Fatal bleeding (bleeding that directly results in death) ○ Perioperative intracranial bleeding ○ Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding ○ Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. ○ Chest tube output >2 L within a 24-h period

Note: TIMI: Thrombolysis in Myocardial Infarction; CABG: coronary artery bypass graft; PRBC, packed red blood cell;

2. Other AEs

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

6.4.1 Definition of adverse events

An adverse event(AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time after the patient has signed informed consent, 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(SAE) is an AE occurring at any dose or during any study phase (i.e., run-in, treatment, and washout, follow-up), that fulfills 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) must be assessed by the investigator(s).

6.4.3 Recording of adverse events

All AE/SAEs will be documented in CRF.

- Time period for collection of adverse events

AEs/SAEs will be collected from the signing of informed consent throughout the study until and including the last visit.

- Follow-up of unresolved adverse events

Any AEs that are unresolved at the last visit in the study are followed up by the Investigator for as long as resolved or keep stable.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- maximum intensity
- Whether the AE is serious or not

- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- 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
- Description of AE.

The definitions for intensity rating are:

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

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 an 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

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should 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 (eg, 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 existing ischemia or death from vascular cause 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 non-serious ADRs and serious adverse events

Investigators are responsible for meeting all regulatory reporting requirements. The investigators are also responsible for reporting SAE to Ethics Committee in time per local requirements.

Investigators must inform the local authority of any SAE within 24 hours in accordance with the local regulations and report SAE to Ethics Committee in time per local requirements.

All non-serious ADRs related to AstraZeneca study drug has to be reported to AstraZeneca Patient Safety within 7 days after awareness by investigator via AZ format form.

All SAEs occur on AstraZeneca study drug have to be reported to AstraZeneca Patient Safety within 24 hours by investigator via AZ format form, whether or not considered causally related to the AZ investigational product. AZ Patient Safety contact information: Fax: +86 21 38683551; E-mail: China.AZDrugSafety@astrazeneca.com; Tel: +86 21 52929866，+86 21 58385073 (Emergency).

6.4.5 Laboratory safety assessment

Table 4: Laboratory tests

Category	Test name
Hematology	Red Blood Cell Count/ Erythrocytes Hemoglobin (Hb) Platelet Count/ Thrombocytes
Coagulation	Partial Thromboplastin Time (APTT) Prothrombin time (PT)
Biochemistry	AST(GOT) ALT(GPT) Protein HbA1c LDL-C Creatinine
Biomarker	cTnT/cTnI

For blood volume see Section 7.1.

6.4.6 Physical examination

A targeted physical examination includes heart and lung.

6.4.7 ECG

12-lead ECG will be performed at screening period and in hospital .

6.4.8 Vital signs

An evaluation of vital signs includes respiratory rate, temperature, pulse rate, and systolic/diastolic blood pressure.

6.4.9 Other safety assessments

Not applicable

6.5 Patient reported outcomes (PRO)

Not applicable

6.6 Pharmacokinetics

Not applicable

6.7 Pharmacodynamics

Not applicable

6.8 Pharmacogenetics

Not applicable

6.9 Health economics

Not applicable

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

Collection of blood samples will be according to regulatory requirements. Approximately 12ml blood for each sample will be taken for analysis of hematology, coagulation, platelet function, biochemistry and biomarker at time points indicated in Table 2 (excluding optional tests).

7.2 Handling, storage and destruction of biological samples

The handing, storage and destruction of biological samples will be in accordance with the requirements of the laboratory in each site.

7.3 Labeling and shipment of biohazard samples

Not applicable.

7.4 Chain of custody of biological samples

Not applicable.

7.5 Withdrawal of informed consent for donated biological samples

Not applicable.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and Chinese GCP. Standard medical care (diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

8.2 Ethics and regulatory review

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP, Chinese GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal trial-related data will be used by principle investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CRA) or Clinical Quality Assurance auditors, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.3 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.4 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigator and Sponsor.

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

The amendment should be approved by each Ethics Committee before implementation. Local requirements should be followed for revised protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.2.

If a protocol amendment requires a change to a centre's Informed Consent Form, Sponsor and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

8.5 Audits and inspections

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

9. STUDY MANAGEMENT

9.1 Training of study site personnel

The PI should ensure adequate training and updated information or notifications have been delivered to study relevant personnels including physicians and nurses.

9.2 Monitoring of the study

9.2.1 Source data

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to

request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For CRFs all data must be derived from source documents.

For paper CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (if available)
- Conclusion of Patient's Participation in the trial

9.3 Study timetable and end of study

- FSI: 06/2014
- LSI: 06/2015
- LSLV: 07/2016
- Report: 10/2016

We anticipate initiation on or before June 2014. We project accrual of 4~5 patients/week, so anticipate the last enrolment by June 2015 and completion of the study by July 2016. We anticipate that these results should be available within 3 months and that a report will be ready for review within 4 months after the end of enrolment.

10. DATA MANAGEMENT

A quality assurance audit/inspection of this trial may be conducted by AstraZeneca or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

The primary endpoint is angiographic vein graft patency by multislice computed tomography angiography(MSCTA) after 12 months.

11.2 Calculation or derivation of safety variable(s)

The major safety variable is incidence of bleeding events. The rate ratio estimate and its confidence limits will be determined.

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.

11.6 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 primary analysis will be done according to the ITT (intention-to-treat) principle. The participants who randomized and have at least one dose of investigational medication will be included. Only the ‘Consent Withdraw’ patients will be excluded which means the patient quit study just after randomization and take no medications. The analysis set according to above principle is defined as modified full analysis set (mFAS).

If there are any other major protocol violations, the corresponding patients will be further excluded from the per-protocol analysis set (PPS) after the adjudication by principle investigator.

12.1.1 Efficacy analysis set

The efficacy analysis will be conducted both on mFAS and PPS.

12.1.2 Safety analysis set

The efficacy analysis will be conducted on mFAS.

12.2 Methods of statistical analyses

Categorical variables will be described by counts and proportions, and continuous variables will be described by mean and standard deviation or median and IQR. Proportions will be compared by chi-square tests or fisher exact test. A Kaplan-Meier (KM) plot of the time to first MACE event in addition to the presentation of KM estimates at 12 months will be provided for each group. Cox proportional hazards model will be used to compare the time to event data between groups. Continuous variables will be compared through ANOVA or Mann-Whitney U tests. A two-sided level of significance of 0.05 is applied to general comparison.

The generalized linear model will be applied to calculate the difference of vein graft patency rate between groups. The difference of patency and its 95% confidence interval will be estimated by the SAS GENMOD procedure and any potential baseline covariates will be adjusted through the model. To avoid the multiplicity issue induced by multiple comparisons among several groups in the primary endpoint, theHochberg method would be used to control the overall alpha level. No multiple testing adjustment will be applided to the secondary endpoints. All analysis will be performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

12.3 Determination of sample size

The study is designed to show the superiority of ticagrelor and ticagrelor plus aspirin as compared with aspirin monotherapy respectively for the 1-year primary efficacy end point of vein graft patency. The primary comparison includes two separate parts. One is to demonstrate T+A better than A and the other is T better than A.

One year rate of vein graft patency in the aspirin group is estimated as 80%. The assumed rate of ticagrelor plus aspirin is 90%. With a two-sided alpha level 0.05 and 80% power, 199 grafts to each group are required. On the other hand, if we assume the rate of ticagrelor monotherapy has the 1-year vein graft patency rate of 87%, under the same two-sided 0.05 alpha 441 grafts in each arm will offer 80% power to show the superiority of ticagrelor along for the primary efficacy end point.

Combined the above two assumptions, if the allocation rate is 1:1:1, this study needs to recruit 1,323 grafts in total (441 in each) to achieve the pre-specified power for both the two comparisons (T+A vs. A and T vs. A).

The principle investigator assumes that the average number of the vien grafts in one patient is 2.7-3.0. With this assumption, 500 patients are to be recruited, which will provide us a total of 1350 - 1500 grafts.

12.4 Data monitoring committee

12.4.1 Image Data Review Center (IDRC)

An independent IDRC will be appointed and will adjudicate all imaging results（grafts failure）. The committee members will be blinded to the treatment group. The precise responsibilities and procedures applicable for the IDRC will be detailed in a separate IDRC charter.

12.4.2 Clinical Endpoint Committee (CEC)

An independent CEC will be appointed and will adjudicate all potential MACE. The committee members will be blinded to the treatment group. The precise responsibilities and procedures applicable for the CEC will be detailed in a separate CEC charter.

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. Treatment of overdose should follow local standard medical practice.

13.2 Pregnancy

If a subject becomes pregnant during the course of the study the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective

termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

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